

THE BRITISH JOURNAL OF DERMATOLOGY

DECEMBER 1960

A FATAL CUTANEO-INTESTINAL SYNDROME.

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THIS case is reported because of remarkable features which seem to make up a definite syndrome. Although it has not proved possible to decide the nature of the underlying pathological process, it is hoped that this case report may lead to the recognition of other cases and the better understanding of their nature.

CASE REPORT.

An unmarried woman aged 61.

Autumn 1957—infection of the gums for which all teeth were removed. At this time there was a lesion on the skin of the nose which healed and left a faint scar. She lost 25 kg. in weight without other symptoms. Laparotomy showed no abnormality.

Summer 1958—an eruption appeared which persisted intermittently until death. December 1958—voice became permanently hoarse.

12 February 1959—first seen at hospital. The skin eruption then consisted of painless discrete lesions evenly scattered over the face, trunk and limbs. Individual lesions were red, infiltrated, round or oval macules up to 2.5 cm. in diameter. After a few days a flaccid superficial bulla developed on the whole surface of the lesion and contained sero-pus. This dried, forming a firm, thick scab which was eventually shed, leaving a very superficial flat scar. The scar became considerably pigmented over the following weeks. The complete evolution of the lesion from first appearance to eventual scarring took three to four weeks. Her general condition was fairly good. Blood pressure 120/65.

Upper respiratory tract (Mr. C. P. Wilson).—The mucosal lesions were scattered on the fauces, pharynx and larynx. There was superficial ulceration in the left vallecula of the tongue, on the lateral walls of both pyriform fossae, at the anterior end of the aryepiglottic fold and on both vocal cords, particularly on the left. There was an area of acute congestion and oedema around each of the areas of ulceration. All the ulcers had a greyish slough. There was no lesion of the genital mucosa.

Investigations.—Chest X-ray normal; Hb 88%; E.S.R. raised (40–66 mm./hr.); W.B.C. 5000 (differential normal); blood culture negative; urine normal; L.E. phenomenon absent; blood urea normal; bleeding and clotting times normal; platelet count normal; urea clearance test 74% of normal; urine contained trace of albumin; Van den Berg, serum bilirubin, thymol turbidity, zinc sulphate, alkaline phosphatase all normal; blood W.R. negative; plasma proteins: slight rise in

alpha-2 globulin; vitamin C saturation 8 days; culture of pus from lesions yielded *Staph. aureus*.

While in hospital under observation in April she developed mild arthritis chiefly affecting the interphalangeal joints. Rose-Waaler reaction negative. There was an irregular pyrexia reaching between 100–101° F. on most nights; normal in the morning. General physical examination revealed no other abnormality.

Course.—She was in hospital from 5 March to 31 May and during that time made a gradual recovery without specific therapy. On 24 June 1959 she was seen as an out-patient and had no complaints.

About 15 July she developed diarrhoea and vomiting. She came to hospital on the 22nd July and was at once admitted. She was moderately dehydrated and her blood pressure varied between 100/60–85/55. No abdominal tenderness or rigidity. No skin lesion. She was passing six to eight loose stools per day but did not vomit any more. The stools contained no occult blood and no pathogenic organisms. Blood urea 54 mg. %, E.S.R. 14 mm. hr. With rest in bed and a light diet her symptoms gradually improved.

On 11 August she had sudden lower abdominal pain with sweating and shock. Blood pressure unrecordable. Laparotomy later that day showed gross generalized peritonitis and bile-stained exudate. A perforation 0.5 cm. in diameter was found in the lower part of the ileum. Adjacent to this, another small ulcer could be seen penetrating as far as but not through the serosa. Three other similar unperforated ulcers were found in the small intestine. The lesions were excised and oversewn.

On 12 August cortisone 600 mg. a day, penicillin and streptomycin were started. General condition slowly improved and continued to improve over the next three weeks. Steroid therapy was continued and gradually reduced to a maintenance level of 35 mg. of prednisone daily. On 27 August skin lesions started to reappear on the trunk and the thighs.

5 September 1959—sudden onset of abdominal pain. Laparotomy revealed gross peritonitis with a large effusion and much fibrin. A punched-out perforation was present in the lower jejunum at the site of a previous ulcer. This was oversewn and the operation terminated because of the patient's poor general condition, without searching for further lesions. Treatment with penicillin was resumed and the dose of steroid increased to 200 mg. of cortisone and 100 mg. of hydrocortisone. In the days that followed her general condition improved very considerably; skin lesions continued to appear and there was moderate, generalized oedema, for which chlorothiazide was given. Her general condition appeared to improve, but on the 23 September she died unexpectedly.

PATHOLOGY.

Biopsies—Skin.—Two biopsies of the skin were carried out in April 1959 and showed essentially the same features. There was a central area of epidermal atrophy with hyperkeratosis and parakeratosis. Throughout the basal cell layer there was marked oedema and immigration of round cells. The cutis showed widespread inflammatory reaction which also extended into the fatty tissue. This was a diffuse infiltration with histocytes, polymorphs and lymphocytes. The histology was compatible with lupus erythematosus, but the possibility of malignant reticulosis could be excluded.

Laryngeal mucosa.—The biopsy material was small and the histological picture not completely satisfactory. The section showed a portion of mucosa with a heavy non-specific inflammatory cellular infiltration. There was no evidence of tumour or of L.E. in this material.

Intestine.—Two ulcers removed at operation were available for histological study. They showed loss of mucosa and extension of the ulcerative process through the

muscularis in places. The cellular inflammatory infiltrate at the margins of the lesions was without special features. In the floor of one lesion was a medium sized arteriole showing inflammatory infiltration with fibrinoid necrosis of the muscularis. Many other vessels visualized in these sections show no abnormality. These appearances suggested a collagen disease.

Post mortem.—Post mortem examination revealed the immediate cause of death as peritonitis and pyaemia, but gave no fresh information regarding the nature of the underlying disease. There was generalized peritonitis with subphrenic and paracolic abscesses and pyaemic infarcts in the lungs and kidneys. The lower part of the small intestine showed the ulcerative lesions which had already been observed at operation and the rest of the intestinal tract was normal.

Histological examination of the kidneys, liver and spleen was otherwise normal and in particular there were no lesions suggestive of disseminated lupus erythematosus or other vascular disease. The histology of the skeletal muscle, adrenals and bone was also normal. Some further skin lesions were examined histologically but yielded no fresh information.

COMMENT.

The course of the disease was not greatly influenced by treatment. The first intestinal perforation occurred at a time when no drugs were being given; the second perforation occurred after 24 days of steroid therapy with a daily dose of 35 mg. of prednisone. Although steroids masked the terminal peritonitis, her general condition was such that recovery from these two major operations seemed unlikely whatever treatment was given. Skin lesions also, after a spontaneous remission, reappeared while she was still on steroid treatment.

DISCUSSION.

From the outset this patient presented a formidable diagnostic problem. When she was first seen the skin lesions had a bizarre appearance and the suggested diagnoses were artefact, drug eruption or reticulosis. These possibilities were soon discounted after a period of observation and investigation, the only positive suggestion being then that the histology of the cutaneous lesion was compatible with lupus erythematosus. The clinical aspect of the lesion however by no means resembled L.E. and although she had some arthralgia and a raised sedimentation rate, there was little positive evidence to support that diagnosis.

When Mr. Wilson saw the mucosal lesions he at once recalled similar rare cases in which fatal intestinal involvement had developed and suggested that this was the likely eventual outcome in this case. This brought to mind the cutaneo-intestinal syndrome to which Degos (1954) gave the name malignant atrophic papulosis. The cutaneous lesion is, however, clearly of different clinical aspect and course. The histology, also, showing much inflammatory change in the present case is very different from the "silent" histology described by Degos. The gloomy prognosis was eventually realized and the patient died despite every surgical facility and skill.

Unfortunately, the detailed records of the previous cases recalled by Wilson are not now available. All of them had lesions of the oro-pharyngeal mucosa, but none of the skin; presumably in this rare syndrome, cutaneous involvement is rarer still. Although the association of skin and fatal intestinal lesions suggests a relationship with Degos's syndrome, this case showed so many points of difference as to be clearly separable.

First, the clinical lesions showed no suggestion of the porcelain-like centre and inflammatory margin so characteristic of the cases of Degos and of the others to which he refers. Second, the skin histology was quite different showing a non-specific perivascular inflammatory change without vascular disease. Third, the intestinal lesions were all apparently ulcers in the first instance which progressed to destruction of the muscularis and in some cases of the serosa. There were no subserous yellow-white patches such as Degos described and the abdominal catastrophe was brought about by perforation which does not seem to be so in Degos's syndrome. Köhlmeier's case (1941) and that of Lausecker (1949) showed prominent peripheral vascular disease upon which the skin and intestinal lesions seemed to depend and led to the suggestion that the whole syndrome was essentially a form of thromboangitis obliterans. Degos does not accept this view but nevertheless recognizes the importance of the vascular lesion. In the present case, vascular changes were not conspicuous and could not be found in the vicinity of most of the lesions examined. For similar reasons the suggestion of allergic vasculitis as the underlying mechanism must be rejected.

At one time the diagnosis of polyarteritis nodosa seemed possible, but here again the histology both of biopsy and post-mortem material completely fails to substantiate this. It is possible to favour a diagnosis of disseminated lupus erythematosus but the argument is chiefly a negative one, supported only by non-specific evidence such as raised E.S.R. and increased serum globulin.

SUMMARY.

A case is reported in which the lesions of the skin and of the oro-pharyngeal mucosa were associated with multiple intestinal ulcers leading to fatal intestinal perforation.

The case appears to be distinct from those of the cutaneo-intestinal syndrome described by Degos.

I am indebted most of all to Mr. C. P. Wilson who recognized the nature of this case and forecast its outcome; and also to Mr. L. P. Le Quesne who undertook her surgical care. Dr. H. Haber and Dr. J. F. Arthur gave valued help in pathology.

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PSEUDO-TUBERCULOMA SILICOTICUM. SPONTANEOUS CLEARANCE OF THE CUTANEOUS LESIONS.

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A CASE of pseudotuberculoma silicoticum with cutaneous changes was described by Sommerville and Milne (1950) with a summary of the previous six reports of this condition affecting the subcutaneous tissues. Their case was treated by surgical removal of all the lesions and subsequent plastic repair. Later in 1950 Sweet demonstrated a patient at the Royal Society of Medicine, London under the title of sarcoidosis following injury and at the same meeting Wells and Goldsmith demonstrated a case as one of tuberculous or silicotic granulomata. Both cases were treated with calciferol, combined with streptomycin in the former.

I can now report on three further cases of a similar nature but with spontaneous healing following diagnostic biopsy. No treatment was given and there was no recurrence in two to seven years. Nodular lesions were present, arising in two of the cases at the site of old injuries. They all showed a tuberculoid picture histologically but doubly refractile, crystalline particles were present.

CASE REPORTS.

Case 1.—A married woman aged 40. Housewife. She presented in 1951 with lesions on the face resembling lupus vulgaris. The lesions were linear and at the site of scars resulting from a motor accident thirty-five years before. A biopsy was performed and the section showed large clumps of foreign-body giant cells surrounded by fibroblasts and lymphocytes. The giant cells contained crystals or amorphous masses of foreign material some of which was anisotropic. She was referred for surgical removal of the lesions and plastic repair. When she reported for this treatment five months after the date of the biopsy, it was found that the conditions had regressed to quite an unexpected degree and only a small indurated area on the upper lip was excised. When seen again nine months after the original biopsy, there was only a bright red telangiectatic patch at the site of the original scars on the right cheek. The area in the middle of the upper lip showed brownish staining and some fulness at the red margin. The biopsy scar could be seen extending down from the right nostril. No further treatment was given and apart from the original scars which are still present, the skin has returned to its former state.

Case 2.—A married woman aged 35. Housewife. My experience with Case 1 made me decide to leave the next such case without treatment and the opportunity arose in 1953 when I saw this patient with a lesion like a basal-cell epithelioma above the left eye. It was yellowish brown, raised one eighth of an inch, with a shiny surface and fine vessels running over the surface. A biopsy specimen was taken and again showed clumps of foreign body giant cells surrounded by fibroblasts and lymphocytes. Crystals or amorphous masses of foreign material, some anisotropic, were present. The lesions had been observed for two months but the patient could

not remember having had an injury or scar in the area. Three months after the diagnostic biopsy, the lower part of the lesion looked depressed, with brownish staining and wrinkled surface. There was at this time a suggestion of faint apple jelly nodules on diascopy. When she was seen nine months after the date of biopsy, the granuloma had disappeared leaving only a fine zig-zag scar in the area. This scar must, I believe, have antedated the granuloma.

Case 3. A married woman aged 39. Housewife. My third case presented in 1956 with an appearance resembling a basal cell epithelioma lateral to the ala nasi, showing as three parallel linear lesions. A second almost circular lesion one third of an inch in diameter was present below the point of the chin. This lesion was situated towards one end of a normally healed scar. She gave a history of injury with scarring twenty-two years before. Three weeks after I originally saw them, the lesions were unchanged and I lightly cauterised that on the chin. As after a further six weeks there was still no change, the same lesion was frozen for two minutes with carbon dioxide snow. Three weeks later, I considered that the lesion at the ala nasi was slightly reduced although this lesion had not received any treatment. A reaction was still present on the chin. After a further six weeks' interval, I considered that the lesions were little, if at all, changed and I took a biopsy specimen from the lesion under the chin. This confirmed the diagnosis of pseudotuberculoma silicoticum, anisotropic crystalline particles being seen. I did not see the patient again until February 1959 and at that time all the lesions had cleared. She reported that the clearing had taken place about three months after the biopsy. She received no treatment of any form following the latter.

DISCUSSION.

Gardner (1932) showed that the introduction of silica into tissues could produce a cellular reaction such as is seen in tubercle. Kettle (1932) suggested that the presence of finely divided silica produced a colloidal solution which acted as a tissue poison. Sweet (1950) made the suggestion of a tuberculous infection in the past with fluctuation of the patient's resistance and reactivity, the patient reaching a state when the presence of the foreign body, introduced some time before, tips the scales against him locally and a tuberculoid focus results. Wells and Goldsmith (1950) suggested that in their case there had been a recent dissemination of tubercle bacilli by the blood stream in a subject whose resistance was good. A proliferative reaction only took place at favourable sites on the skin, namely those scars that probably contained some silica. Sommerville in the discussion on this case suggested a specific tissue response occurring in a peculiar subject probably of the tuberculous type. In Sweet's case there was no suggestion of tuberculosis at any time in the past, but in that of Wells and Goldsmith there was a past history of tuberculous cervical glands from which tubercle bacilli had been recovered. My three cases had no family or personal histories of tuberculosis and radiography of the chest in all three showed a normal picture. Gland biopsies were not undertaken.

The interesting response to the minor surgical trauma of biopsy is, I feel, evidence against the suggestion that these cases were basically tubercular. I have not seen a similar sequel to biopsy in cases of lupus vulgaris or sarcoid.

I appreciate that we commonly see this sequel to biopsy in the case of granuloma annulare but the histological picture in this condition is very different to that of pseudo-tuberculoma silicoticum. I believe that the response to biopsy adds strength to the suggestion of a specific reaction to the foreign body, but I can offer no explanation of the mechanism of the response. If we accept that silica was present in the granulomata before biopsy, then, as only a part of the granuloma was removed and as granulomata at other sites were not subjected to any interference, silica must have remained present in the tissues after this minor surgical procedure. Yet all the granulomatous reaction subsided even in those areas quite far removed from the site of the biopsy.

There was a strong clinical resemblance between the lesions in the three cases. While apple jelly nodules were seen on diascopy, as was to be expected from the histology, the superficial appearance in two of the cases was more that of a basal cell epithelioma. In the first case the appearance was that of lupus vulgaris. The outline of the lesions in all cases, however, was artificial, linear or bizarre. Where a scar was present, diagnosis was simple but even in the case where no scar was evident at the first examination, the clinical appearance immediately suggested the diagnosis.

SUMMARY.

Three histologically confirmed cases of pseudo-tuberculoma silicoticum are described.

Clinically, one case presented the appearance of lupus vulgaris and two that of basal cell epithelioma.

No treatment was given. All three cases cleared a few months after the diagnostic biopsy and have not recurred during an observation period of two to seven years.

I am very much indebted to Dr. J. E. Craik of the Pathology Department, the Victoria Infirmary.

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TORULOSIS PRESENTING IN A SKIN DEPARTMENT.

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TORULOSIS is uncommon in England although it is being more frequently recognized. Skin lesions are not rare, but very unusual as the presenting feature of the disease. We feel justified, therefore, in presenting such a case in a 45-year-old man who had never left England. The infection disseminated and proved fatal. At post-mortem examination, unexpected evidence of lymphadenoma was found. The response to amphotericin-B (Fungizone, Squibb) was another point of interest.

The causative organism of torulosis (European blastomycosis) is a yeast-like fungus, *Cryptococcus neoformans* (*Torula histolytica*): it occurs throughout the world. It affects men more commonly than women and is most common in the fifth and sixth decades. The portal of entry appears usually to be the respiratory tract. Any organ of the body may be involved, but there is a predilection for the lungs and the nervous system. In the brain the lesions may be meningeal or parenchymal. Cryptococcal infection is much more common in people with lymphadenoma and other malignant conditions of the reticulo-endothelial system (Annotation, *Brit. med. J.*, 1957, Symmers, 1957). Not only is there an increased incidence of torulosis in these conditions, estimated at 1 to 10%, but there is also increased dissemination. Torulosis is also occasionally associated with sarcoidosis.

The fungus is an oval or round, thick-walled organism 5 to 15 μ in diameter. It possesses a characteristic wide refractile capsule which is more obvious in indian ink preparations. It reproduces by a simple budding process. It grows at 37° C. or at room temperature, although growth may not be obvious for several days. On Sabouraud's medium the colonies are at first white and granular, but later become moist, mucoid and buff. Biopsy material shows granulomatous lesions with many organisms which can be identified by the wide capsule. The lesions may be confined to the brain and meninges, or to the lungs: the infection may become generalized.

Altogether, over twenty cases have been recorded in England. Most of these have been reported in the last fifteen years. It may be occurring more frequently: it is certainly being recognized more commonly. It has been found in people who have been abroad and also in others who have never left England.

Skin and mucous membrane lesions have occurred in many of the British cases, but in no recorded case have skin changes been the presenting feature,

except in one, reported by Symmers (1953), of a man aged 27 with Hodgkin's disease of two years' duration, who developed multiple facial ulcers. These were at first thought to be rodent ulcers, but histological examination showed them to be due to cryptococcal granulomata. The nervous system became involved and the condition proved fatal. Johns and Attaway (1933) described a case of torula meningitis following a razor cut, at which site a cryptococcal granuloma developed. When secondary to lesions of the pulmonary or nervous system, the skin changes are variously described as acneiform, nodular, granulomatous or ulcerative.

Until recently, the results of treatment have been poor, 85% of patients dying within a year. Vaccines, sulphonamides and the antibiotics were of no value, although Marshall and Teed (1951) reported an apparent cure in a girl aged eleven years using sulphadiazine and potassium iodide. Actidione seemed of limited value (Appelbaum and Sinovij, 1957). Nystatin proved valueless, 2-hydroxystilbamidine was little better. Amphotericin-B, (derived from *Streptomyces nodosus*) however, seems of definite value. It seems more potent than the related compound amphotericin-A. It is of no value orally and has to be given intravenously (Symmers and Winner, 1959 ; Rubin and Furculow, 1958). The usual dosage is 0.25 mg./kg. daily (increasing rapidly to 0.5-1.0 mg./kg. daily), well diluted with 5% dextrose.

CASE RECORD.

A man aged 45, who worked in a copper refinery as a furnaceman, was admitted complaining of multiple ulcers on the face and neck (Fig. 1). These had developed over the previous nine months. He also complained of mild occipital headache of recent onset. He had not vomited and had no symptoms referable to the respiratory system. On examination he looked ill, but apart from the multiple ulcers the only abnormal sign was slight hepatomegaly. The facial ulcers were grossly infected: the early lesions before ulceration were umbilicated. While in the ward he became drowsy and his behaviour abnormal. The ulcers continued to enlarge and fresh lesions developed. His general condition deteriorated and by the eighteenth day after admission it appeared that he would die within the next few hours.

When the possible diagnosis of a fungus infection was first raised griseofulvin 1 g. daily was started. To this were added potassium iodide and nystatin. None of these drugs appeared to have any beneficial effect. When the diagnosis of cryptococcosis was definitely established, treatment was started with amphotericin-B (0.25 mg./kg. daily rising to 0.5 mg./kg. daily). The patient's condition soon improved: on the second day of treatment he spoke for the first time for a week and recognized his wife for the first time for several days. The ulcers became smaller and much cleaner. Unfortunately the improvement was maintained only for a few days and he died suddenly on the tenth day of treatment. We are sure, however, that he would have died several days sooner had it not been for the treatment with amphotericin-B. Earlier administration might have been life-saving.

The only untoward effect of the amphotericin was a mild rigor during the administration of one of the doses. The blood urea remained steady: serum electrolyte levels remained normal until the day of death. Pyrexia was never marked and was absent after the first day's treatment.



FIG. 1.

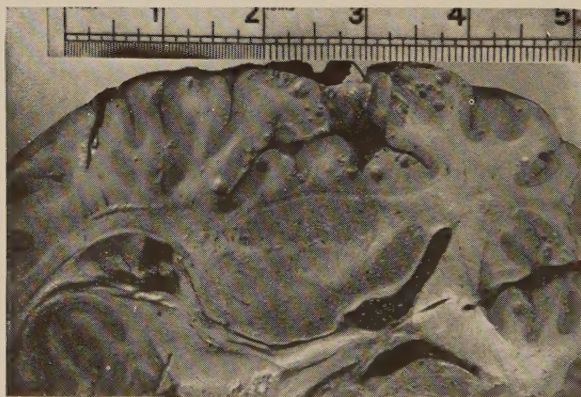


FIG. 2.

Investigations.—Many investigations were undertaken: the more important were as follows. Hb, 83%, E.S.R., 19 mm. hr., blood cultures, sterile, W.R., negative. Urine, trace of albumin: a few "yeast" cells in deposit: growth of *Cryptococcus neoformans*. Swabs from ulcer also grew cryptococci. C.S.F., 5 cells per ml., protein 300 mg.%, excess globulin, culture yielded cryptococci. Skiagrams. Skull normal: chest, "There is a little shadowing in the right middle lobe probably due to fibrosis, but there is no evidence of any recent or active pulmonary disease. Cardio-vascular shadow is normal." Histological examination of a biopsy specimen from a facial ulcer showed cryptococcal granulation tissue.

Autopsy.—(Dr. A. H. Cruickshank, Dr. B. Blewitt) revealed a solitary cryptococcal granuloma in the upper lobe of the right lung and extensive granulomatous invasion of the parenchyma of the kidneys, adrenals, prostate and brain (Fig. 2). The meninges were normal apart from small areas deep in the sulci. The parenchyma was studded with small cystic areas of granulomatous reaction with plentiful cryptococci. There were numerous nodules up to 1 cm. in diameter in the liver and spleen which showed unsuspected but typical lymphadenomatous invasion on section, as did the mediastinal lymph glands.

SUMMARY.

A 45-year-old man with torulosis presented with skin lesions. He died despite treatment with amphotericin-B. At autopsy he was found to have unsuspected lymphadenoma.

We are grateful for help received in this case from Prof. W. St. C. Symmers and Dr. A. H. Cruickshank and for the generosity of E. R. Squibb and Sons Limited in providing supplies of amphotericin-B and secretarial help. This case was briefly reported in the Record of the North of England Dermatological Society (1959) p. 63.

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PEMPHIGOID TREATED WITH CORTICOSTEROIDS.

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The days of our age are threescore years and ten : and although men be so strong that they come to fourscore years : yet is their strength then but labour and sorrow : so soon passeth it away and we are gone. (Psalms, 90, 9.)

PEMPHIGOID is a disorder which predominantly attacks those whose age is over threescore years and ten and in the days before the introduction of steroid therapy, the prognosis was as poor as the above quotation implies. Civatte's (1943) work on the histological differences between pemphigus and pemphigoid was made known in this country by Rook and Whimster in 1950. In the succeeding three years, the clinical picture and prognosis of pemphigoid was described. One such series of eleven patients (Church, 1953) with an average age of seventy-four years included seven fatalities, most from bronchopneumonia. In 1952, corticotrophin became available and was used in those cases encountered from 1952 to 1954. In 1954, cortisone became the drug of choice. In an account of the use of these steroids in eleven cases of pemphigoid (Sneddon and Church, 1955) the average age was seventy-seven years and there were four deaths. Not only did steroid treatment reduce the death rate, but rapid control of the disease diminished the extent of blistering, making it possible to mobilize the patients more rapidly and to shorten the duration of their stay in hospital.

Eight years have passed since steroids were first used in these cases : many of the patients were already well past their allotted span and the first purpose of this paper is to review the fate of these aged patients on prolonged steroid therapy. Secondly, the advantages of prednisolone therapy as seen in a further twenty-one patients are reviewed. Of the total of thirty-seven patients treated with steroids, eighteen were submitted to biopsy. Histological examination of the specimens revealed a subepidermal bulla with no acantholysis in each case.

TREATMENT AND COURSE.

Corticotrophin and cortisone.—During the years 1952 to 1956, eight patients were treated with corticotrophin and eight with cortisone. The age of these sixteen patients ranged from 64 to 86 years with an average age of 75 years. The dose necessary to control the disease ranged from 20 to 50 mg. of ACTH gel ; or 100 to 400 mg. of cortisone daily.

Four of these patients died within a few weeks of admission to hospital with the eruption still uncontrolled, death being due to pulmonary emboli in two cases, mesenteric thrombosis in one and hypostatic pneumonia in another. The only other serious complication in the initial stage of treatment was a pulmonary embolus followed by pneumonia in a woman aged 65 who fortunately survived. The two oldest patients aged 86 continued on a maintenance dose of ACTH gel and remained well for 10 months and 14 months before dying of bronchopneumonia. A patient aged 79 at the commencement of the disease in 1954 was later maintained on prednisolone, 15 mg. daily, and remained well for 4 years before dying of apoplexy in 1958. Another patient aged 80 when the disease was treated in 1953, has not been traced and is presumed dead.

Seven patients remain well. Their present ages range from 71 to 84 years, with an average of 77 years. They have been maintained on steroids for from three to seven years. Although initially treated with corticotrophin or cortisone, five now receive prednisolone in a dose of 5 to 10 mg. daily, and another cortisone 50 mg. daily. A woman now aged 71, who was maintained on cortisone for three years, has remained well for a further two years without treatment.

The following case is typical.

A woman aged 68 developed an eczematous eruption on the limbs in September 1949 which became bullous eight weeks later. The eruption went away after admission to hospital, but she suffered from chronic bronchitis and each subsequent winter the bullous eruption flared up when her chest became troublesome, unrelated to therapy. In 1953, histological examination of a blister showed the characteristic subepidermal bulla of pemphigoid. In October 1953, she was first treated with ACTH gel and went into a remission without a maintenance dose until 1955. She then had a further attack of blistering which recurred when corticotrophin was stopped and required a maintenance dose of ACTH gel, 20 mg. five times weekly.

In February 1956, cortisone 100 mg. daily was substituted and in 1957, prednisolone. She is still maintained on the latter in a dose of 5 mg. twice daily. Now a very frail old lady of 80 with severe chronic bronchitis and congestive cardiac failure for which she receives mersalyl injections, she is still able to get about and to visit the out-patient department on foot.

Prednisolone. Since 1955, twenty-one patients suffering from pemphigoid have been treated with prednisolone from the onset of the disease. There were eleven men and ten women between the ages of 48 and 90 years, the average age being 73. The disease was brought under control in all these patients, but four of them died a few weeks after treatment. One of these was a man of 62 who was suffering from cardiac failure following a coronary thrombosis before the onset of pemphigoid. Despite severe cardiac failure, his eruption was controlled by 40 mg. of prednisolone daily and he survived on a maintenance dose of 30 mg. daily for four months before dying of cardiac failure. The other three patients who died early in the course of treatment were aged 90, 84 and 79 years; the disease was controlled, but one patient died of cerebral thrombosis,

a second of bronchopneumonia and in the 90-year-old, the cause of death was not established. Two further patients have died since having started steroid therapy, one from gangrene of the foot after a year's treatment. The other, a man of 66, commenced treatment in January 1957, five weeks after the onset of his eruption. Blistering was controlled with prednisolone 40 mg. and ACTH gel 10 mg. daily; eventually he required a maintenance dose of 15 mg. of prednisolone daily. Four months after commencing treatment, he was admitted to another hospital for investigation of dyspepsia, prednisolone was stopped and the eruption did not recur. It later transpired that the cause of his dyspepsia was a carcinoma of the stomach from which he died in January 1959. During the twenty months which he survived after stopping steroids, there was no recurrence of the skin eruption. One other patient aged 87 at the onset of his eruption in 1957, has not been traced and is presumed dead.

The other fourteen patients remain well. Two stopped treatment after 6 and 10 months respectively and have remained well for 4 and 2 years. The remainder receive a maintenance dose of prednisolone which varies from 5 to 30 mg. daily. Ten of these patients were first treated in the years 1956-58 when their average age was 74 years, despite which they have survived from 2 to 4 years.

Controlling dose.—The side effects of salt and water retention produced by corticotrophin and to a lesser extent by cortisone made massive doses dangerous in the aged and the few failures in those days were probably caused by having to strike a balance between a dose which controlled and one which caused side effects. With prednisolone, the eruption has been controlled in every case and few have required a very high dose of steroids. When a high dose of prednisolone has been reached without complete control of the eruption, it has been my practice to add a small dose of ACTH gel; partly because this has been thought to prevent complete inactivity of the adrenals and partly because this seems to be more effective than continuing to increase the prednisolone. Four cases required over 50 mg. of prednisolone daily; three were treated by the addition of ACTH gel 20 mg. daily and one was given 60 mg. of prednisolone. They were two men aged 48 and 67 and two women aged 57 and 60 years: they therefore included the three youngest patients in the whole series, which suggests that the younger the patient, the more fulminating and refractory the disease. Once the latter is controlled, even a high dose can gradually be reduced and the maintenance doses in these four patients range from 10 to 30 mg. of prednisolone daily.

Table I summarizes the details of the cases described.

Ambulant treatment.—At one time it was almost essential for patients suffering from this disease to be admitted to hospital, since blistering and erosion of the skin over large areas of the body made the nursing problem similar to that of extensive burns. In the pre-steroid era, most dermatological wards

TABLE I.—*Summary of the Series.*

	Group from pre-steroid era, 1948-52 (Church, 1953).	Group treated with ACTH and/or cortisone 1952-56.	Group treated with prednisolone 1955-59.
Number of cases . . .	11	16	21
Age range (years) . . .	59-89	64-86	48-90
Average age (years) . . .	74	75	73
Number of cases dying with active pemphigoid	7	4	0
Causes of death . . .	Pneumonia, 3 Pyæmia, 1 Cerebral thrombosis, 1 Undetermined, 2	Pulmonary embolus, 2 Mesenteric thrombosis, 1 Pneumonia, 1	
Controlling dose mg./day . . .	—	Cortisone, 400 ↓ ACTH gel, 20	Prednisolone, 60 and ACTH gel 30 ↓
Maintenance dose mg./day . . .	—	ACTH gel, 40 ↓ Cortisone, 50 ↓ nil	Prednisolone, 20 Prednisolone, 30 ↓ nil

contained one or more of these patients who lingered in hospital for months before eventually dying of the disease. The introduction of corticotrophin shortened their stay in hospital and reduced the death rate, but the need for caution in dosage still meant that the eruption could become troublesomely widespread and entail many weeks in hospital. The introduction of prednisolone with less risk of side effects has enabled us to use a higher dose from the start of treatment and the disease has been even more rapidly controlled. Six of the twenty-one patients treated with prednisolone have either been seen at home or treated as ambulant out-patients. In all cases the disease was diagnosed in its early stages when blistering was not more extensive than could be dealt with by a daily visit of the District Nurse. The disease was complicated by the presence of severe hypertension in two cases, congestive failure in a third and mountainous obesity in another. Despite these adversities, all six patients remain well under the care of their general practitioners and have been free from the eruption for periods of up to eighteen months.

Side effects.—"Moon face" has been present to some degree in all patients. It seems probable that the high incidence of thrombosis in the corticotrophin and cortisone series was significantly associated with the steroid therapy. Hypertension which was severe in one patient was increased by the controlling dose of prednisolone, 40 mg. daily, but reverted to its usual level when the maintenance dose was reduced to 20 mg. daily. Dyspepsia and peptic ulceration have not occurred in any case. Analysing a series of the published cases of various diseases tested with steroids, Nordin (1960) found a 20% incidence of dyspepsia in 385 cases and 4.5% peptic ulceration in 630 cases. It therefore

would appear that dyspepsia and peptic ulceration is less likely to occur in those over the age of sixty.

COMMENT.

The use of prednisolone has changed the course of pemphigoid from that of a prolonged, distressing and often fatal illness to that of one which can be completely controlled in a few weeks and which, if diagnosed in its early stages, need not necessitate admission to hospital. In those few patients attacked by the disease in the sixth decade, control may be difficult and it is advisable to use a high dose of prednisolone at the start of treatment. In the older age groups, the eruption is usually more easily controlled and they tolerate prolonged steroid therapy with a low incidence of side effects. Indeed, it is my impression that quite apart from controlling the disease, in many of these old people steroid therapy appears to prolong life rather than to shorten it. In this series, only four patients have stopped treatment and have remained in remission.

In a series of sixty-eight patients with pemphigoid collected from eleven London teaching hospitals, Stevenson (1960) found that thirty were able to stop treatment eventually, minor relapses occurring in only two.

SUMMARY.

The fate of the survivors of a group of sixteen patients treated for pemphigoid with corticotrophin and cortisone is analysed.

Twenty-one patients have been treated with prednisolone since 1955; the disease was controlled in all and fourteen patients are still well.

It is suggested that if the disease is diagnosed sufficiently early, ambulant treatment with the patient remaining at home is the most satisfactory way to avoid complications in these elderly patients.

I am grateful to my colleague Dr. I. B. Sneddon for allowing me to quote cases observed under his care.

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ELECTRON MICROSCOPIC OBSERVATIONS ON PEMPHIGOID

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SINCE the first electron microscopic examination of thin sections of human skin by Adolph, Baker and Leiby (1951), substantial technical improvements have taken place, so that there are now a number of adequate studies in the literature (Selby, 1955, 1956, 1957; Charles and Smiddy, 1957; Charles, 1959; Charles and Ingram, 1959; Odland, 1958; Clark and Hibbs, 1958; and Hibbs and Clark, 1959). These have understandably been concerned with normal skin and the study of pathological material has barely begun. The lesion of molluscum contagiosum, however, has been well studied (Banfield and Brindley, 1959; Dourmashkin and Bernhard, 1959 and Charles, 1960*a*); observations have been made on the wart virus (Bunting, 1953; Charles, unpublished) and Darier's disease (Charles, 1960*b*). Psoriasis, pityriasis rubra pilaris and the Ehlers-Danlos syndrome have also been studied, but the results are not readily accessible (Charles, 1958).

The present paper is concerned with a case of pemphigoid and is published largely to supplement the results of light microscopic studies with the greater clarity of those of electron microscopy. No unexpected findings have been made.

INVESTIGATION.

A biopsy specimen was removed from the proximal part of the dorsum of the left foot of a man aged 79 years, suffering from pemphigoid. The smallest observable blister was chosen for removal. It was about 1.25 mm. long by about 2 mm. wide; one of its long edges was delineated with gentian violet. After local anaesthesia by the injection of 2% procaine containing 1:40,000 w/v adrenaline, a biopsy specimen 1 to 2 mm. wide was cut so that the gentian violet line ran down its centre. By cutting the specimen at right angles to its long axis, small blocks of tissue were obtained each including part of the edge of the blister. This was done with a razor blade after the material had been placed on cork slightly moistened with veronal buffer. The pieces were transferred to a chilled 1% solution of osmium tetroxide made in the same veronal buffer of approximately pH 7.4. Fixation commenced about 5 minutes after injection of the anaesthetic and continued for two hours in the refrigerator, being completed by standing for another two hours at room temperature.

After washing and dehydration in ethyl alcohol, pieces of the tissue were infiltrated with *n*-butyl methacrylate monomer containing 1% benzoyl peroxide, or with "Araldite" epoxy resin as recommended by Glauert, Rogers and Glauert (1956) and Glauert and Glauert (1958). The infiltration with methacrylate was carried out in the usual manner, finally embedding in a thin methacrylate syrup at 80° C. according to the recommendation of Borysko (1956). The Araldite infiltration was carried out by standing for one hour periods in 1:1 and 1:3 mixtures of absolute

alcohol and Araldite at room temperature, followed by three one hour changes of Araldite at 80°. In the last of these changes, the accelerator specified by the manufacturers had been added to the resin. The tissue was then transferred to a foil boat (Borysko, 1956) containing fresh Araldite and accelerator and allowed to stand at room temperature overnight. Polymerization was completed by leaving at 80° for the following day.

The material was sectioned on a modified Cambridge rocking microtome using glass knives and examined on carbon-filmed copper grids in a Metropolitan Vickers E.M.3 electron microscope.

RESULTS.

A marked difference can be seen between the cornification of the skin forming the blister and that of the adjacent "normal" skin. Fig. 1 shows the granular and horny layers from the "normal" skin. The keratohyalin granules and the appearance of the cells in general exhibit no gross abnormality. The only departures from normal are the increase in the number of layers in the stratum granulosum exceeding five in the original micrograph, and a few cornifying granules which are assumed to be an abnormal form of keratohyalin, and are responsible for the round spaces (*gs*) which appear in the maturing squames. The cell boundaries, demarcated by prickles (desmosomes), show no evidence of oedematous distension.

Part of the roof of the blister is shown in Fig. 2. Horny and granular layers are located respectively above and below a line drawn roughly from the top left to the bottom right corners of the figure. The keratohyalin in the granular layer is entirely in the abnormal form and is identifiable in the young cornified squames as discrete particles generally separated from the squame contents (the corneoplasm, see Charles, 1959) by a surrounding space. Although most of the cells in the granular layer show little distortion of their boundaries by intercellular oedema, marked distension is seen between some of the upper cells and between the cornified squames. Even more severe distensions were frequent, but cannot be illustrated here. The greatly disorganized cell (*Ic*) with a shrivelled, degenerating nucleus seen among the cornified squames is not a dermal cell carried to the surface but an epidermal cell, identifiable by its prickles, which is cornifying rather later than its neighbours.

A malpighian cell with distended prickles is shown in Fig. 4. There is much dense granular material, presumably RNA, in the cytoplasm, together with larger, possibly vesiculate, structures, numerous mitochondria and tonofibrils, many of which are transversely sectioned. The intercellular regions are free of debris, suggesting that there is little protein in the intercellular fluid.

Fig. 3 illustrates the dermo-epidermal junction, which runs from the top left corner to about the middle of the right-hand side of the figure; the epider-

mis is uppermost. Along this length of junction the oedema has not proved sufficient to force apart the dermis and epidermis, though oedematous channelings are seen as clear spaces in both. There is evidence of intercellular distension in the epidermis and the mitochondria are greatly swollen. Although the wall-membranes of the basal cells are observable, the junction has a coarse, damaged appearance compared with that found in normal skin (see Charles and Smiddy, 1957). The fibrous tissue is very abnormal: it appears to have degenerated into an undifferentiated mass, for neither striated collagen nor elastin fibrils can be distinguished. In the dermis there are numerous infiltrating cells, predominantly eosinophilic leucocytes. Generally the cytoplasm of the eosinophils is undergoing lysis, so that it is often possible to discern individual eosinophilic granules scattered amongst the fibrous tissue; such granules are not well shown here. Occasionally eosinophilic leucocytes are seen in the epidermis. One of the basal cells shows the precocious formation of what appears to be keratohyalin of the abnormal type predominant in Fig. 2.

Fig. 5A shows the beginning of separation between dermis and epidermis at the very edge of the bulla. There is a clean separation between the two, although occasionally some dermal tissue adheres to the basal cells. In the epidermis, which is on the left, much intercellular distension is shown, while swollen mitochondria and abnormal keratohyalin are again present. The ragged appearance of the outer surfaces of the basal cells suggests erosion of the cell wall-membranes.

Part of an eosinophilic leucocyte is shown in Fig. 5C. The characteristic granules are evident, but there are also irregularly shaped granules which may be related in some way to the basophilic bodies shown by Low and Freeman (1958). The external cytoplasmic membrane of the cell seems to be disintegrating, presumably because the cytoplasm itself is being dissolved.

Fig. 5B is a section of the abnormally cornified squames, in which discrete structures, presumably incompletely cornified mitochondrial remains, are detectable instead of the relatively homogeneous corneoplasm normally found. The remnants of former prickles also are evident.

DISCUSSION.

From these observations it is not possible to implicate subtle intercellular changes as the cause of the pemphigoid bulla. Dermis and epidermis alike are affected by the oedema which, presumably at a point of greater pressure, forms the bulla by causing separation along the dermo-epidermal junction. Prior to this ultimate separation, the junction is damaged by the oedematous changes, so that it comes to have a ragged appearance. The surface of adhesion between dermis and epidermis, normally seen in sections as a moderately dense

line (Charles and Smiddy, 1957) is destroyed; the basal cell membrane sometimes survives, but may often be badly eroded. A comparatively normal appearance of the junction was observed in the "normal" region of the present material, even though this "normal" material was within one millimetre of the edge of the blister. Where oedema is seen, the oedematous spaces are generally free from precipitated debris, suggesting that the fluid contains little protein. It is noteworthy that although they are severely stretched, the intercellular attachments at the prickles never show evidence of breaking apart (acantholysis). This contrasts with other skin lesions, e.g. molluscum contagiosum (Charles, 1960a) where considerably less marked oedema is frequently attended by such breakage.

The obliteration of the fine details of the fibrous dermal tissue, so that it becomes a rather dense, poorly differentiated mass, is probably a consequence of the alteration, or precipitation, of the ground substance. It would be interesting to know more specifically what takes place, but as yet the electron microscope yields little information. Appearances suggest that the collagen is in a fine fibrillar form within the mass and does not develop into the more robust fibrils of normal skin. Elastin has not been observed. Individual

EXPLANATION OF FIGURES.

Explanation of figures. *bb*, basophilic bodies; *cg*, cornifying granules; *e*, eosinophilic leucocyte; *eg*, eosinophilic granules; *em*, eroding cell membrane; *gs*, spaces left in horny cell by failure to incorporate the cornifying granules into the corneoplasm; *gm*, granular material (RNA); *hc*, horny cells; *j*, dermo-epidermal junction; *kh*, keratohyalin, *lc*, late cornifying cell; *m*, mitochondria; *mc*, marginated chromatin; *n*, nucleus; *no*, nucleolus; *od*, oedematous distensions; *p*, prickle (desmosome); *pr*, prickle remnant in cornified cell; *sm*, swollen mitochondria; *t*, tonofibrils; *vm*, vesiculate material.

The small dense dots seen in some of the figures (most obviously in Fig. 5A, B) are particles of gold sol, about 15 $m\mu$ diameter, used as an aid to focusing (Flewett and Tymms, 1956). The illustrations are all of the methacrylate embedded material, except Fig. 4, which shows the Araldite embedded material.

FIG. 1.—Showing the upper granular layers and lower horny layers in "normal" epidermis outside the blister. The keratohyalin is of normal appearance, but there are a few cornifying granules in the prickle cells, the presence of which is responsible for the circular spaces (*gs*) in the horny cells. $\times 4500$.

FIG. 2.—Upper granular layers and horny layers in the epidermis of the blister roof. Cornification granules, and intracellular distension of prickle and horny cells by oedema, are present. Precipitated material is observable in some of the distended spaces in the granular layer. $\times 3000$.

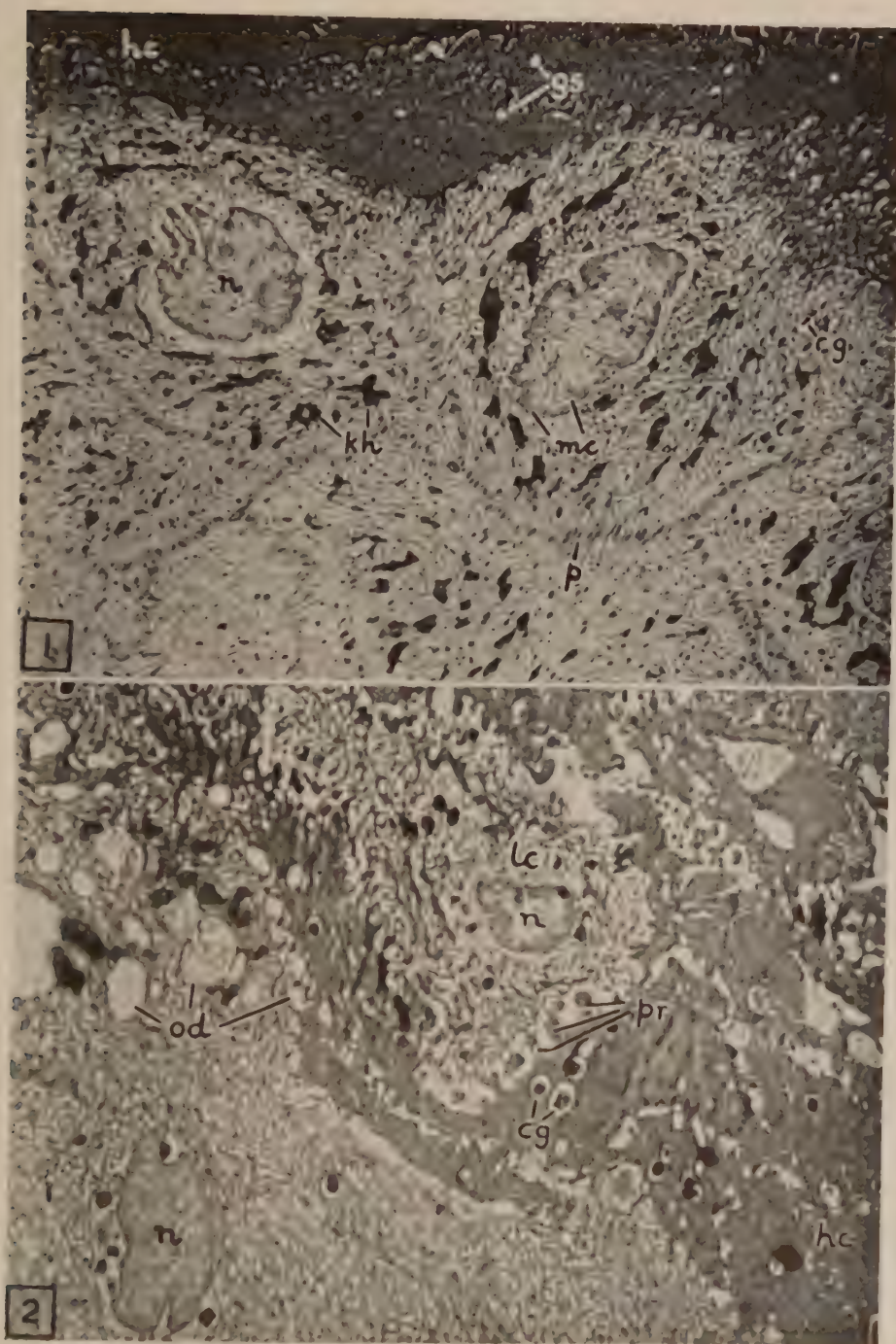
FIG. 3.—Showing the abnormal appearance of the dermo-epidermal junction caused by the oedema whose presence is evident from the clear spaces occurring in the dermis and epidermis. Many eosinophilic leucocytes with their characteristic granules are seen in the dermis. $\times 3000$.

FIG. 4.—Two Malpighian cells, showing the stretching of the prickles between them by intercellular oedema. $\times 18000$.

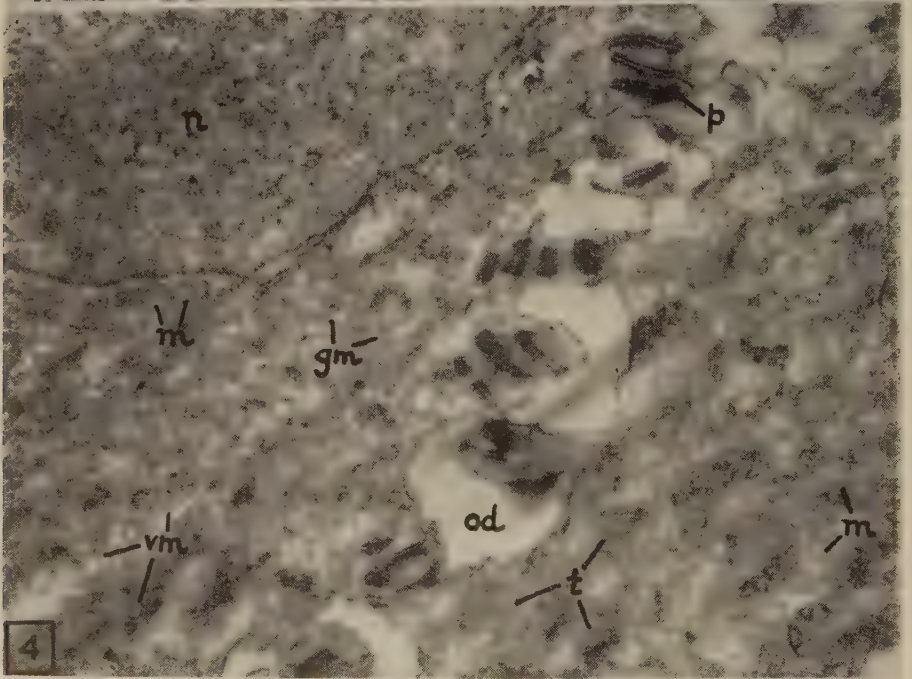
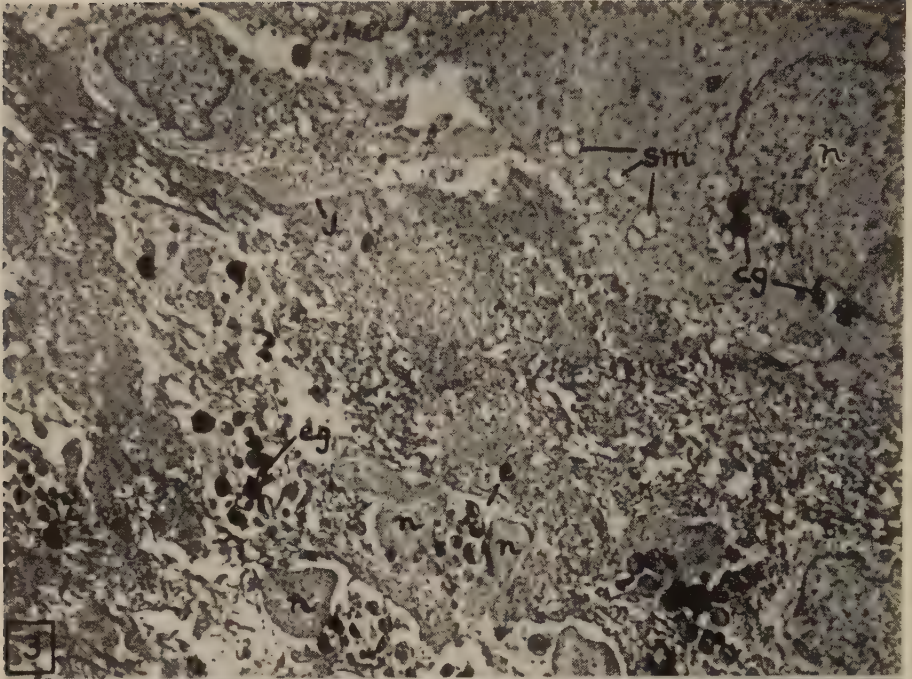
FIG. 5.—A. Showing the separation of dermis (right) and epidermis (left) at the edge of the blister. The fine structure associated with the normal dermal fibrous tissue has been obliterated and the outer membrane of the basal cells appears somewhat eroded. $\times 5000$.

B. Showing discrete structures (possibly mitochondrial remnants), oedematous spaces, and prickle remnants within the fibrous background of the cornified squame contents. $\times 27000$.

C. Part of an eosinophilic leucocyte showing eosinophilic granules and other structures which are possibly basophilic bodies. The outer membrane of the cell is disintegrating. $\times 9000$



FIGS. 1 and 2.



FIGS. 3 and 4.

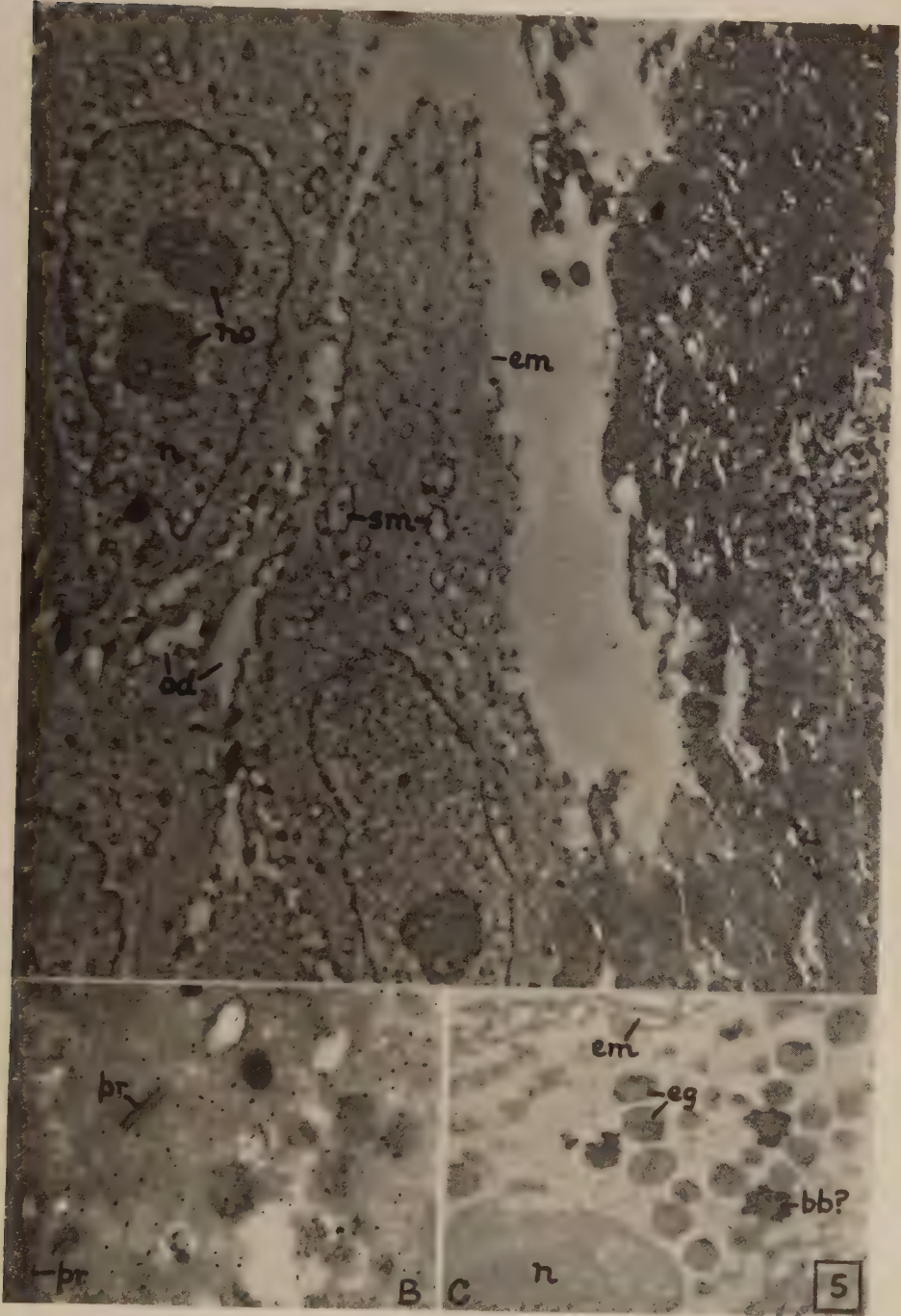


FIG. 5.

granules of eosinophils survive the disintegration of the cytoplasm in which they were originally located and are commonly seen scattered through the dermis. Is it possible that they release a secretion which affects the course of blister formation?

The increase of cytoplasmic detail, i.e., of granular and vesiculate material, with an increased number of more robustly constructed mitochondria, shown by the Malpighian cells of Fig. 4, is commonly observed in pathological material. The unusual appearance of the prickles stretched by intercellular oedema in the same figure is probably the result of sectioning through opposed cell boundaries which have been thrown into sharp convolutions by the distensions.

The precociously formed cornifying granules and the retention of discernible structures within the advancedly cornified cell are commonly seen in dyskeratotic material, but no precise biochemical explanation can yet be given to account for them.

SUMMARY.

A description is given of the electron microscopic appearance of skin changes taking place in the blister of pemphigoid. No unusual information has been obtained and no specific intracellular changes are seen. The dermo-epidermal junction is damaged by the oedematous changes which eventually cause its cleavage. Obliteration of the fine structure of the dermal fibrous tissue suggests the precipitation or alteration of the ground substance; the collagen probably remains in a very fine fibrillar form. Elastin is not seen. There is intercellular oedema of the epidermis, and the epidermal cells show increase of cytoplasmic detail—i.e., an increase in granular (RNA) and vesiculate material, increase in the number and robustness of mitochondria which, presumably when the cell is further damaged, may become greatly swollen. Dyskeratosis is indicated by the precocious formation of cornifying granules (which is not specific) and the retention of observable structures, possibly mitochondria, within the cells showing advanced cornification.

It is a pleasure to thank my colleague, Dr. N. R. Rowell, Senior Registrar in the Skin Department of the General Infirmary at Leeds, for his determination to eliminate many obscurities in the original draft of this paper.

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LICHEN PLANUS AFTER LIGHTNING STROKE.

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THE aetiology of lichen planus is obscure. A typical generalized case in which the rash appeared two days after the patient was struck by lightning is reported.

CASE RECORD.

A Bantu boy aged five years was standing near an open door in his home during a thunderstorm. His mother was also in the room, cooking at her coal stove. There was a bright flash and a scream and the child was hurled six feet across the floor and under the stove. His eyes were open and he made coarse generalized jactatory movements. He could not be roused and on being spoken to made no response. This state persisted for approximately an hour, towards the end of which he began to sweat profusely and vomited once. When he regained consciousness, he complained of stomach ache and weakness, and all his muscles were flaccid. Two small blistered areas were present on the left side of his chest. A rash appeared quite suddenly two days later.

Four weeks later he was transferred to my care. His general health was good but from the neck down he had a wide spread eruption of flat violaceous papules, in some places aggregated into plaques. His mother was not present and no history was obtainable; I had no knowledge of what had happened until she came to take him home. The unusual feature was the extent of the eruption. There was little of the trunk or limbs that was spared. On the flanks and sides of the chest the arrangement of the lesions was linear and parallel to the ribs, but over the abdomen they were almost confluent. On the upper thighs the lesions ran obliquely inwards. In general, the pattern of Langer's lines was closely followed. On the front of the left thigh an example of the Koebner phenomenon was present, a group of lesions following the line of a scratch. The "blisters" described by the mother were no longer present.

A biopsy specimen showed hyperkeratosis and an increase in the granular layer. There was a dense, sharply defined, lymphocytic infiltrate in the papillary and subpapillary layers and the line of demarcation between the dermis and epidermis was less distinct than usual.

The child was given cortisone acetate 25 mg. b.d. for four weeks and at the end of this period the main residual abnormality was dark bluish-black pigmentation at the sites of the previous lesions.

Was it mere coincidence that lichen planus appeared so shortly after the accident? Many people have been struck by lightning, and have lived, and although arborescent skin markings are a feature of such cases (Glaister, 1947) no one to my knowledge has reported that they have developed lichen planus. On the other hand, many authors discussing the aetiology of the disease make prominent mention of "upsets in the nervous system". (e.g. Sutton, 1956; Pillsbury *et al.*, 1956). I have always interpreted this to mean psychological upsets. Would it be more correct to extend the conception to include any or all factors which sufficiently disturb the physiological activities of the nervous system?

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AMMONIATED MERCURY POISONING.

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I. THE ABSORPTION OF MERCURY FROM OINTMENTS.

It is remarkable that in spite of the frequent use of ammoniated mercury in ointments, little attention has been paid to the possibility of poisoning by its absorption through the skin. Reports of such cases are rare (Alexander and Mendel, 1923 ; Frühwald, 1928 ; de Levie, 1938 ; Oertel, 1940 ; Williams and Beach, 1950 ; Warkany and Hubbard, 1951 ; Hengeveld, 1951 and Hermans, 1956). It is therefore not surprising that ammoniated mercury continues to be used in dermatology. However, the results of the investigation described below make one marvel that so few cases of intoxication have been described. This may be because too little attention has been paid to the occurrence of solitary symptoms of poisoning during treatment. Once we began to look for them, we recognized a great number of isolated toxic symptoms in our own patients who were being treated with ammoniated mercury.

Some authors have tried to find out whether psoriasis caused disturbances of liver function. In most cases, no abnormality could be detected by means of liver function tests. In some patients, however, in spite of normal tests, abnormalities were found on microscopical examination of liver biopsies. These consisted of fatty infiltration and discrete foci of necrosis (Huriez *et al.*, 1957 ; Gertler, 1958). Occasionally, cirrhosis and subacute hepato-cholangitis were seen. Such changes could have been caused by mercury, since practically all patients suffering from psoriasis are treated for some time with ointments containing it, especially as ammoniated mercury. (Mercury may originally have been added to tar preparations to prevent folliculitis, but it is not clear why ammoniated mercury should be the almost invariable choice). Little attention has been paid to the absorption of ammoniated mercury through the skin. Moreover, most of those who have done so based their conclusions on small numbers of observations (Maloff, 1928 ; Moncorps, 1930 ; Grossenbacher, 1936 ; Robert, 1946 and Gibbs *et al.*, 1948). After studying the main literature on this subject, Rothman (1954) concluded that among all mercurials in use for external treatment, ammoniated mercury was absorbed least through the skin.

The most important investigation on this subject was carried out by Inman *et al.* (1956). They determined the excretion of mercury in the urine of twelve patients suffering from psoriasis who were treated for six weeks with an ointment

containing 2% ammoniated mercury. Six excreted 300 γ /l. after being treated for some weeks. In two patients, excretions of more than 1000 γ /l. and one patient even 1500 γ /l. were observed. In none of these were symptoms of intoxication observed. The investigation, however, was carried out on out-patients who could not be supervised as closely as is possible with patients admitted to hospital.

The maximum excretion of mercury which is harmless is variously stated. The normal daily excretion of mercury is only 5–10 γ in faeces and urine together and is caused by ingestion with food (Borinski, 1931). An excretion of more than 300 γ a day is generally considered to be dangerous, as this would usually be accompanied by symptoms of poisoning (Bidstrup *et al.*, 1951). It must be emphasized, however, that a low excretion of mercury does not exclude the possibility of intoxication (Zangger, 1930; Brezina, 1932; Neal *et al.*, 1937; Jordi, 1947; Agate and Buckell, 1949; Ledergerber, 1949 and Warkany and Hubbard, 1951). Moreover after the administration of some organic mercurials, scores of milligrams of mercury can be found daily in the urine without symptoms of poisoning. One must assume that these mercurials do not ionize or do so only slightly; a high excretion of mercury is of little clinical importance in such cases.

INVESTIGATION.

A large number of determinations were made of mercury in the urine of patients suffering from psoriasis and who were being treated with an ointment or paste containing 10% ammoniated mercury. The method described by Leach *et al.* (1956) was employed. The urine is broken down with sulphuric acid and potassium permanganate, and extracted with a solution of di- β -naphthyl-thiocarbazon (DBN) in chloroform. Both mercury and copper are bound as a complex by the latter and can be determined together colorimetrically. The chloroform layer is then extracted with thiosulphate, by which the mercury-DBN complex is destroyed. The colour which is left in the chloroform layer is then due exclusively to copper.

Altogether about 400 determinations were made. From these it appeared that during normal in-patient treatment, requiring for adults about 100 g. a day of an ointment containing 10% ammoniated mercury, urinary mercury excretions of 500–1000 γ /l. are found, whereas daily excretions in the order of some milligrams are not exceptional (Table I). From the data obtained in this way the following may be concluded:

(i) A clear connection exists between the amount of the mercury excreted and the duration of treatment with ammoniated mercury.

(ii) If the excretion of mercury is extremely high, symptoms of intoxication may be expected; in other respects a clear relationship between the amount of the mercury excreted and the appearance of toxic symptoms does not exist.

(iii) During out-patient treatment, the excretion of mercury is much less than during in-patient treatment; undoubtedly this is due to the unwillingness

TABLE I.—*Urinary Excretion of Mercury in Selected Patients.*

Age (years).	Sex	Quantities of ammoniated mercury ointment used			Excretion (γ /l.)		Period of observation (weeks).	Symptoms of intoxica- tion.
		Daily amount (g.).	%	Duration (weeks).	Mean.	Maximum.		
36	F.	90	10	6	800	2000	6	—
65	M.	100	10	4	2800	5000	4	+
39	"	100	10	4	1200	1500	4	+
15	F.	80	10	3	2000	3400	3	+
30	M.	80	10	2	500	850	2	+
11	F.	60	10	2½	1400	3600	6	+
39	M.	40	10	3	400	500	8	+
10	"	40	10	3	150	450	3	—
52	"	40	10	2	40	100	2	—
53	F.	60	10	2	400	550	10	+
49	M.	60	10	1	150	200	4	—
50	"	25	10	1½	800	1500	5	—
69	"	80	5	½	200	700	6	+

The mercury determinations in the urine have a reliability of ± 10 –15%.

of patients to apply an ointment intensively at home. Frequently it is used only at night.

(iv) Considerable absorption of mercury takes place, even if only a small area of skin is treated, e.g. the scalp, but the extent of the treated surface (related to the quantity of ointment) seems to influence the excretion of mercury.

(v) Great differences in excretion of mercury exist between individual patients. A clear connection between the amount of the mercury excreted and age and sex of the patients does not exist.

II. SYMPTOMS AND SIGNS OF MERCURY POISONING DUE TO THE USE OF OINTMENTS.

From these facts it is obvious that a considerable amount of mercury is absorbed through the skin after application of ointments containing ammoniated mercury and more cases of intoxication are to be expected than one would assume from the literature on this subject.

INVESTIGATION.

To investigate this, all patients with psoriasis who were treated as in-patients in the Dermatological Department of the State University of Utrecht over a period of two years were investigated. On admission, the investigation included general physical examination, blood picture, urine tests for albumen, reducing substances, urobilin, sediment and power of concentration, liver function tests, estimation of the creatinine content of the blood and patch tests with 10% ammoniated mercury and 10% liquor picis carbonis separately and together, all in soft paraffin.

Except where contraindicated, the patients were treated with preparations containing 10% each of ammoniated mercury and liquor picis carbonis, to the scalp

as an ointment whose base consisted of equal parts of lanolin and soft paraffin, elsewhere in zinc paste. The ointment or paste was applied once a day and successive applications were made on top of the old, without removing the latter. As a rule the anointed areas were not bandaged. A bath was taken twice a week. Some patients were also given a mixture containing sodium thiosulphate.

During treatment, the following examinations were performed: the volume of urine was determined daily. The urine was examined daily for the presence of albumen and urobilin, and if the former were found the sediment was also examined. It was examined now and then even if no albumen were present. Determinations of mercury in the urine were performed as frequently as possible. Attention was paid to the possible appearance of symptoms of intoxication.

At the end of treatment the patients were re-examined in the same manner as on admission. Measurements of the daily volume of urine and the determinations of mercury were continued, if possible, for some time after treatment had ceased. If during treatment abnormalities or symptoms had been encountered, the patients were observed and the examinations continued for as long as was rational.

Altogether, 70 patients were observed and of these 33 had symptoms or signs of mercurial intoxication. As it is often difficult to distinguish between toxic and allergic reactions, all side-effects attributed to mercury are mentioned. Eleven patients had albuminuria, which was prolonged in two cases and temporary in nine. There were four cases of erythroderma and two of contact dermatitis. Thirteen patients complained of abdominal symptoms, eleven during combined treatment with ammoniated mercury ointment and the mixture containing sodium thiosulphate, two during the use of the ointment alone. Eight patients complained of headache, four of nausea, two of dizziness, one of hyperhidrosis and two of precordial pain. Five developed gingivitis or bleeding gums and one purpura and nose bleeds. One patient showed conjunctivitis and keratitis and another complained of a metallic taste in the mouth. One developed tremors, but only one neuritis. There was a single instance of haematological changes (anaemia, leucopenia, eosinophilia), but abnormalities of liver function tests were detected in seven. In six of these, the alkaline phosphatase content of the blood was elevated and in five a positive urobilin reaction in the urine was regularly found. This also occurred in a further seven cases where the liver function tests were otherwise normal.

Patients with disturbed liver function tests particularly had an elevated alkaline phosphatase content of the blood. It is known that intoxications may cause a so-called cholangiolitis and consequently an elevated alkaline phosphatase content of the blood (Verdonk, 1949). This determination therefore appears to be important in these patients. Isolated urobilinuria does not always point to a disturbance of the liver function: urobilinuria may also be a symptom of several other diseases (Bruins Slot, 1956). The appearance of urobilinuria therefore has a limited diagnostic value. In some cases, however, especially in combination with other findings, it may be an important sign, when it may be considered as a delicate and simple test of liver function. It was observed in a number of patients that the urobilin reaction of the urine

became positive during treatment with the mercurial ointment and negative again after it.

It is striking that mental disorders were never observed among our patients and a definite neurological disorder only once ; some authors are of the opinion, however, that disorders of the central nervous system can only be caused by prolonged contact with certain mercurials, mostly organic (Zangger, 1930 ; Byrne, 1947 ; Bürgener, 1952 ; Hughes, 1957). Formerly 40% of felt hat makers developed mercury poisoning from handling mercuric nitrate, hence the expression "as mad as a hatter".

III. THE THERAPEUTIC VALUE OF AMMONIATED MERCURY.

As the application of ammoniated mercury to the skin is followed by considerable absorption and consequently by symptoms of mercury intoxication, one must consider whether the therapeutic advantages of ammoniated mercury justify this risk. The main indication for the use of ammoniated mercury is psoriasis and for this purpose, it is frequently used in combination with liquor picis carbonis.

A further investigation was therefore carried out to determine whether the ammoniated mercury could be omitted from this combination without loss of therapeutic effect. It also seemed interesting to answer the following questions. Is ammoniated mercury or liquor picis carbonis the stronger antipsoriatic? Is the therapeutic effect of an ointment with ammoniated mercury and/or liquor picis carbonis considerably better than the effect of the vehicle alone? Has the vehicle itself also a therapeutic effect and, if so, is there any difference between a paste and an ointment? Is it possible to replace ammoniated mercury with an organic mercurial?

INVESTIGATION.

The best method of investigating the therapeutic effect of an ointment is the method of paired comparisons (Siemens, 1942 ; v. Czetsch-Lindenwald and Schmidt-La Baume, 1950). First, I investigated whether ammoniated mercury or liquor picis carbonis were the stronger antipsoriatic. For this purpose the therapeutic effect of 20% ammoniated mercury in zinc paste on the right side was compared with 20% liquor picis carbonis in zinc paste on the left side in 25 patients. In 16 cases no difference between left and right could be observed and in 9 the ointment with liquor picis carbonis proved better. In no case was the result better with the ointment containing ammoniated mercury. It is therefore probable that liquor picis carbonis has a somewhat better therapeutic effect than ammoniated mercury.

I then investigated whether the combination of ammoniated mercury and liquor picis carbonis in an ointment had a better therapeutic effect than one with liquor picis carbonis alone. For that purpose, in 20 patients the therapeutic effect of a combination of 10% ammoniated mercury with 10% liquor picis carbonis in zinc paste on the left side was compared with 10% liquor picis carbonis in zinc paste on the right side. In no case was the effect on the left side better than that on the right. It is very unlikely that the addition of ammoniated mercury to an ointment which already contains liquor picis carbonis is useful.

Further, it was investigated whether the addition of ammoniated mercury and/or liquor picis carbonis to zinc paste gave a better result than zinc paste alone. The therapeutic effect of ammoniated mercury and/or liquor picis carbonis in zinc paste was compared with that of zinc paste alone in 16 patients. In all cases there was a distinct difference in favour of the mercury and/or tar therapy.

It seemed interesting to discover whether the vehicle itself had a therapeutic action, and whether there was a difference between those of zinc paste and soft paraffin. In all 10 cases investigated the vehicle had an obvious therapeutic effect. Further, it appeared from paired comparisons on 15 patients that zinc paste was distinctly better than soft paraffin: in 13 cases the former was clearly better and in 2 there was no difference.

An attempt was made to establish which substance in the zinc paste was responsible for its superior action. A paste containing 40% starch in soft paraffin was compared in 13 cases with a paste with 40% zinc oxide in the same base, but there was no obvious difference. Starch, zinc oxide or perhaps merely the physical properties of the application may be responsible for its therapeutic action.

I also tried to replace ammoniated mercury with an organic mercurial, i.e. Merfen (Zyma) or Riasol (Shield Laboratories). Wyss-Chodat (1941) reported some good results from the use of Merfen on patients with psoriasis, as did Voss (1953) with Riasol, but neither used the method of paired comparisons. I compared the therapeutic effect of 0.02% Merfen (the strongest concentration possible for use on the skin) in zinc paste with that of 10% ammoniated mercury in zinc paste in 10 patients. In one case irritation was seen from Merfen, in 5 there was no difference between the two applications and in 4 ammoniated mercury was better. As Riasol is a liquid, I compared this with an indifferent shake lotion which had no therapeutic action. The results with this substance were also disappointing; of 14 patients, 8 showed minimal difference in favour of Riasol and in 6 there was no difference. If there was a difference, it was much smaller than the difference between an indifferent shake lotion and zinc paste and it is probable that the use of zinc paste is preferable. Moreover, in 5 of these cases irritation of the skin was caused by Riasol.

The most important conclusion from the results of these paired comparisons was that it seemed very probable that ammoniated mercury could be abandoned in the therapy of psoriasis without difficulty. To be sure about this a statistical analysis of the main results was performed.

The chance that the combination of liquor picis carbonis and ammoniated mercury gave a better result than the former alone is at most 17%.* In patients who obtained no better result with a combination of liquor picis carbonis and ammoniated mercury than with the former alone (thus at least 83% of all patients), the chance that liquor picis carbonis alone gave a better result than in combination with ammoniated mercury was at most 17%. The chance that ammoniated mercury gave a better result than liquor picis carbonis was at most 15%. In patients, who obtained no better result with ammoniated mercury than with liquor picis carbonis (thus at least 85% of all patients), the chance that liquor picis carbonis gave a better result than ammoniated mercury was between 17 and 58%.

These observations suggest that ammoniated mercury is best avoided in the treatment of psoriasis.

* Every conclusion has a reliability of 95%.

SUMMARY.

The excretion of mercury in the urine of patients who were being treated with an ointment containing ammoniated mercury was determined.

During normal in-patient treatment with this ointment, urinary excretions of mercury of 500 to 1000 γ /l. were found and daily excretions of several milligrams were not exceptional.

Seventy cases treated for psoriasis as in-patients with ammoniated mercury were carefully examined before, during and after treatment; thirty-three showed symptoms or signs of mercury poisoning.

Paired comparisons showed that ammoniated mercury was not indispensable for the treatment of psoriasis and organic mercurials were of no value.

The use of ammoniated mercury for the treatment of psoriasis is therefore to be avoided.

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BOOK REVIEWS

A NEW FRENCH TEXTBOOK.*

THE publication of a new textbook by one of the most distinguished teachers of the St. Louis school is an important event in the world of dermatology. Professor Duperrat's *Précis de Dermatologie* is a remarkable contribution to medical literature, which will deservedly take its place among the classics of clinical dermatology, yet it is unusually difficult to review it critically and objectively. Both its merits and its defects are inherent in the traditions of the French School, and the book will therefore be enthusiastically welcomed by francophils among whom the present reviewer numbers himself, but may be less warmly received by the detractors and critics of the School.

The *Précis* is a handsome quarto of 1106 pages: the design and typography maintain Masson's customary impeccable standards. There are over 500 of M. Maire's excellent photographs, appropriate, informative and well reproduced. The literary style is easy and fluent, personal and informal, verging on the conversational and a pleasure to read. The text is divided into two sections in the manner of Darier's *Précis*: in the first, dermatoses are considered from the morphological and in the second from the aetiological aspect. The material is skilfully marshalled and arranged to avoid repetition. The second section also includes chapters on special topics such as skin disorders of the newborn and topographical dermatology. A formulary and an adequate index complete the work.

The emphasis throughout is clinical and practical. The clinical descriptions are admirable and are enlivened by brief summaries of personal cases to illustrate features of interest and importance. Differential diagnosis is also very effectively covered as the author's rich experience has enabled him to confine himself to the essential and practical problems, and to avoid the formidable and improbable lists of conditions not seriously deserving consideration which disfigure some textbooks.

Dr. Duperrat is well known for his contributions to histopathology and it was therefore to be expected that the pages devoted to this subject would be particularly helpful. Some of these sections might well have been more detailed, but all are lucid and accurate. There are useful tables of histological differential diagnosis; those dealing with "nodular vasculitis" and with the bullous eruptions are noteworthy.

It is the sections on aetiology and on treatment which may arouse some criticism. The author is obviously thoroughly familiar with the world literature and eschews narrow chauvinism, but surely recent investigative work justifies a more ruthlessly critical approach than he sometimes chooses to adopt. This is of greater importance in the evaluation of theories of pathogenesis than in the recommendation of therapeutic procedures. Some of the latter are not commonly employed in Britain, but in this country we are perhaps too inclined to prefer therapeutic nihilism to what we choose to regard as "unscientific" treatment, and even to reject well-tried medicaments on the sole grounds of their empiricism. Dr. Duperrat's views on treatment may be read with interest and profit.

There can be few dermatologists, however great their experience, who would not enjoy this outstanding volume, and who could fail to find it stimulating and informative. It is a book for the specialist rather than the student and is a book to be read and not exclusively a work of reference. It is to be hoped that its merits will ensure

* *Précis de Dermatologie*. B. DUPERRAT (1959). Paris: Masson. Pp. 1106. 565 illus. Price 19.200 francs.

the preparation of a second edition and that the author will then take the opportunity to correct an important omission. Many hundreds of authorities are cited but in only a few instances is the reference included. This omission is particularly frustrating when the authority's name is unknown to the reader and the statement attributed to him is of special interest.

A. J. R.

PIGMENT CELL BIOLOGY.*

THIS is the report of the Fourth Conference on the Biology of Normal and Atypical Pigment Cell Growth held in November 1957 at Houston, Texas. It follows the pattern of the reports of the First and Third Conferences (*Biology of Melanomas*, 1948, and *Pigment Cell Growth*, 1953) and like these volumes is edited by the late Myron Gordon who was a specialist in fish genetics. The two previous books made a world-wide impact and publicized the advances which had been made in the study of pigmentation since the time of Bruno Bloch.

In this book Szabo points out that melanocytes are always present in the basal-cell layer of normal human skin and scars and also in the squamous epithelia of the mouth and nose. In all parts of the body each malpighian cell is in contact with more than one melanocyte. The term naevus cell (he thinks) should be abolished since these cells are melanocytes. In most pathological conditions with increased melanin formation the increase is the result of a stepping up in the rate of pigment production and not of an increase in the number of melanocytes. Pinkus *et al.* confirm this notion in their studies with Thorium X. Zimmermann and Becker examined fifty-four negro foetuses and suggest that the generalized but temporary "bed" of immature melanocytes in the human dermis is similar to the permanent layer of active melanocytes in anthropoid apes and some monkeys.

There are a number of contributions dealing directly and indirectly with pigment cell tumours. According to Fitzpatrick and Kukita, all but two of the regions in the body where melanocytes occur are known to be the primary sites of malignant melanomata. There are, however, no reports of melanomata arising in the hair bulb or retinal pigment epithelium (the latter being anatomically and embryologically distinct from the choroid). The tyrosinase activity of these two loci must therefore be under rigid control. Chang, Speece and Russell suggest that tyrosinase activity is the most promising clue to the diagnosis and treatment of melanomata. The experiments of Chase and Hunt show that x-ray damage to pigment cells is proportional to oxygen tension. These findings may be of therapeutic significance. Hormonal control of melanogenesis is discussed by several contributors. Dalton and Krassner describe darkening of the skin when the pituitary of a white axolotl larva is replaced by that of a dark one. When the experiment is done in reverse the dark axolotl larva does not become lighter. Melanomata in the Syrian hamster are darkened by the injection of melanocyte stimulating hormone, but beef pineal extract has the opposite effect (Foster). Stress comes into most things these days and pigmentation is no exception. Goldfish darken under stress, but only if the pituitary is intact (Chavin). The biochemistry of melanin is discussed by Mason, who suggests that the brown humus of soil is a melanin. The colouring of butterflies and other insects and of molluscs derives from a series of pigments known as the omnochromes (Forrest). These are made from tryptophane and are therefore chemically closer to the yellow pheomelanin than to brown melanin which is made from tyrosine.

The book contains numerous illustrations including electron microscope photographs of pigmented and unpigmented melanocytes by Birkbeck and Barnicott. The

* *Pigment Cell Biology*. Edited by MYRON GORDON (1959). New York: Academic Press. Pp. 647. Price \$13.50.

value of a publication like this is that it gathers together information which would otherwise remain scattered in numerous specialist journals. It also contains reports of discussion between people who would not otherwise meet.

J. S. P.

SYMPATHECTOMY.*

THIS book is based on an intensive, long-term study of more than fifty sympathectomized patients. Return of autonomic function has been most carefully assessed by testing both sudomotor and vasomotor activity. Dr. Monro's work is already well known to surgeons and neurologists but may be new to many dermatologists. He starts with the advantage of a combined approach—that of an anatomist and that of a clinical neuro-surgeon. He is thus able to avoid many of the errors of interpretation that have so often marred work on this subject. He examines this work in some detail and brings forward persuasive physiological and anatomical reasons to explain earlier discrepancies. He emphasizes, for instance, the importance of the previously neglected intermediate ganglia to explain the different sweating patterns induced by autonomic stimulation and by "mecholy". Of particular interest also to dermatologists are the sections on the "escape" sweating areas of the face and perineum that are not affected by sympathetic section and those on gustatory sweating and the auriculo-temporal syndrome. The author examines the conflicting findings and explanations offered in the past about this syndrome and advances an ingenious explanation for it and for the phenomenon of central facial sweating.

The section on "Clinical Applications" is limited by space but Dr. Monro makes several points of importance to those who may be called on to advise patients on this operation. The results of sympathectomy on hyperhidrosis of the hands, for instance, is better than that of the feet, because a partial return of function gives an acceptable degree of moisture to preserve the grip. Conversely, Raynaud's disease needs a perfect result, and this rarely occurs. In assessing the effects of sympathectomy in various disease Dr. Monro regrets the "complete absence of any objective post-operative study of the influence of autonomic denervations".

This book—which is surprisingly easy to read and extremely well documented—will remain the definitive work on the subject for many years. It will also remain a model of the value of a combined physiological, anatomical and clinical study, correlated by one person who can interpret the observation made in each discipline to explain the whole. It should find a place in the library of every large dermatological department and be read by all who are interested in autonomic innervation.

D. S. W.

THE FRENCH ENCYCLOPEDIA.†

THE latest issue of this encyclopaedia introduces a new plan. Previously, periodical supplements have been issued in various subjects which have often caused the reader considerable research to find all he wanted. Now each subject is being dealt with comprehensively and systematically so that over a period of three years a complete review of dermatology with nearly two hundred coloured pictures will be published. The first article on purpura may be used to illustrate the new form. It starts with a discussion on modern theories of coagulation and haemostasis followed by a survey of a wide series of relevant tests. The physiopathology of purpura

**Sympathectomy. An anatomical and physiological study with clinical applications.* P. A. G. MONRO (1959). London: Oxford University Press. Pp. 290. Price 75s.

†*Encyclopédie Medico-Chirurgicale.* (1959). Issue Nos. 54-55, Special Volume 36-37, Dermatology. Paris: Éditions Techniques.

follows and this includes a long list of drugs known to produce purpura ; finally there is a section on the clinical aspect and treatment. Subjects similarly dealt with *in extenso* include psoriasis, eczema, acne, leg ulcers and vascular tumours by well-known authors from all over France. The articles are well illustrated both in black and white and in colour and contain a good representative bibliography drawn from international sources. This new venture represents an important contribution to French dermatological literature and one which should be available in every dermatological department. Such a collection should start at once with the current volume.

F. F. H.

ATOPIC CATARACT.*

THE clinical characteristics of atopic cataract are only too well known to any practising dermatologist or ophthalmologist. All else, however, remains obscure, in spite of a wealth of material. It would be surprising, therefore, if the examination of ten cases by means of a slit-lamp added greatly to our knowledge. In fact, the resulting monograph of 102 pages with 107 references and 18 illustrations (none of the skin) in the main only reproduces available information and even that with little attempt at critical appraisal. For instance, the possibility that the ocular lesion may derive from previous radiotherapy is canvassed in the following sentence, which is a good example of both the author's style and his approach to scientific discipline - "While no laboratory or clinical affirmation has been forthcoming, the theoretic incrimination and the investigative intuition of some observers clamour for open-minded awareness of this possibility".

P. F. B.

AN AMERICAN FORMULARY.†

THE second edition of this book follows the method used in the first to a large extent. Chapters are devoted to modalities of treatment of selected diseases or to groups of drugs, the whole arranged in alphabetical order, thus "Acne Preparations" are followed by "Anesthetics for Topical Use". In many ways it may be described as a pharmacopoeia devoted to drugs of use in dermatology.

The book reflects the advances in treatment which have taken place during the six years since the first edition was published. This applies particularly to the steroids both local and general, the use of antimalarials in lupus erythematosus and the tranquilizers.

One can offer few criticisms on the work which tries to explain the mode of action of the drugs mentioned and gives the structural formula of many of them. The authors consider this important especially in relation to cross sensitivities. The American nomenclature is not such a drawback as it was in the earlier edition, because alternative names are given for most drugs and many of the more important are now known by the same names in England as they are in America. Nevertheless it is doubtful if many copies will be sold in this country.

P. D. S.

* *Atopic Cataract*. E. ROSEN (1960). Springfield : Charles C. Thomas, Oxford : Blackwell Scientific Publications. Pp. 102, illus. 18. Price 46s.

† *Dermatologic Medications*. M. R. LERNER and A. B. LERNER (1960) 2nd Edition. Chicago : Year Book Publishers, London : Interscience Publishers. Pp. 208. Price 45s.

CURRENT LITERATURE

THE FATTY ACID COMPOSITION OF THE SURFACE SKIN FATS IN ACNE VULGARIS AND SEBORRHOEIC DERMATITIS. B. BOUGHTON, R. M. B. MACKENNA, V. R. WHEATLEY and A. WORMALL. (1959) *J. invest. Derm.*, **33**, 57.

Using the same method as reported in the previous paper no alteration from normal was detected in the composition of surface lipid fatty acids of patients with acne vulgaris. Nor was there any change during pregnancy in a patient with acne despite improvement of her skin condition.

In one of four cases of seborrhoeic dermatitis the proportion of unsaturated fatty acids was significantly lower than in normal subjects, and there was a return to normal after treatment.

Hairless rats showed no change in the composition of surface fats as a result of feeding chocolate and pork fats. Therefore no evidence was forthcoming of the reputed deleterious action of these foods.

(This is certainly one of the most important recent contributions to our knowledge of acne. The fact that the composition of the sebum in acne is not altered, clearly shows the disturbance of the sebaceous glands in the condition to be quantitative rather than qualitative.) A. J.

AN ELECTRON MICROSCOPE STUDY OF CORNIFICATION IN THE HUMAN SKIN. A. CHARLES. (1959) *J. invest. Derm.*, **33**, 65.

This paper described the changes seen by electron microscopy during the process of keratinization. The author found that keratohyalin is deposited on the tonofibrils of the granular cells. In the cells above this region the electron opacity of the keratohyalin granules is lost, but this is associated with a comparable increase in the opacity of the cell walls. It is suggested that there may be a transference of electron dense material from the granules to the walls of the cell. He also suggests that the nodules in the prickles surrounding the keratinized epidermal cells contain the hardest keratin. (This is a useful paper on the investigation of a dynamic process in the skin studied by electron microscopy. There is also evidence from light microscopy and chemical analysis in support of his hypothesis that cell walls within the stratum corneum are well keratinized.)

A. J.

DECREASE IN HUMAN HAIR COLOUR AND FEATHER PIGMENT OF FOWL FOLLOWING CHLOROQUINE DIPHOSPHATE. T. S. SAUNDERS, T. B. FITZPATRICK, M. SEIJI, P. BRUNET and E. E. ROSENBAUM. (1959) *J. invest. Derm.*, **33**, 87.

It is reported that an inhibition of yellow-red pigment formation in the Rhode Island Red fowl, but not in the Black Minorca is the result of injecting chloroquine into the yolk sac of six-day-old eggs.

This suggests that the inhibitory effect of chloroquine is not by way of the tyrosine-melanin pathway, but due to its effects on the yellow-red pigment formation. The nature of this metabolic block was not elucidated.

A. J.

SMALLPOX VACCINATIONS IN THE MANAGEMENT OF RECURRENT HERPES SIMPLEX: A CONTROLLED EVALUATION. A. B. KERN and B. L. SCHIFF. (1959) *J. invest. Derm.*, **33**, 99.

One group of patients with recurrent herpes simplex was treated with multiple smallpox vaccinations; another was treated with heat inactivated vaccine. Of those given the active vaccine 67% remained free from attacks during the follow-up period which averaged 20 months. Of those given the heat inactivated vaccine 52% remained free. Since there is no significant difference in these two groups there appears to be little real benefit from this form of therapy.

A. J.

THE TECHNOLOGY OF IN VITRO STAINING OF NERVES IN HUMAN SKIN WITH THIAZIN DYES. R. P. ARTHUR and W. B. SHELLEY. (1959) *J. invest. Derm.*, **33**, 121.

This paper reviews the historical use, and chemistry of the thiazin dyes. It describes a new technique for nerve staining. (This method is rather involved and the reviewer's trials have not been entirely satisfactory.)

A. J.

HISTOLOGY AND CYTOCHEMISTRY OF HUMAN SKIN. XIX. THE DEVELOPMENT AND FATE OF THE AXILLARY ORGAN. W. MONTAGNA. (1959) *J. invest. Derm.*, **33**, 151.

The writer describes the natural history of the apocrine sweat glands. He studied 150 specimens of axillary skin from fetuses and subjects of all ages.

These glands develop in the fifth month of intra-uterine life as appendages of the axillary hair follicles.

They begin to function at 8 years, and at this age resemble the glands of adults. No specific morphological changes were found during the menstrual cycle or during pregnancy. A. J.

STUDY OF CUTANEOUS MICROBES BY THE CELLOPHANE ADHESIVE STRIP METHOD.

H. M. JETTMAR. (1959) *Derm. Wschr.*, **140**, 893.

The cornified cells, as well as the microbes present in the horny layer, can be detached in layers with the aid of cellophane strips. After culture of these strips on blood agar small colonies emerge which give an indication of the quantity as well as of the localization of the microbes in the tissues.

Then the incubated strips are brought into contact with a glass slide and stained. This appears to be a quick and convenient method for assessment of the bacterial colonies from different layers of the epidermis.

There seems to be a considerable variation in the bacterial flora in different patients as well as different cutaneous areas of the same patient. J. M.

A CASE OF MORBUS KYRLE. A. B. JÖRNBERG. (1959) *Derm. Wschr.*, **140**, 899.

A typical case that was not influenced by vitamin A and prednisolone therapy. CO₂ snow treatment, however, was beneficial (after removal of hyperkeratotic lesions). The treatment had to be repeated in some instances. The histology of an apparently healed lesion, however, showed still the characteristic picture. J. M.

CEMENT ECZEMA. St. STOYANOFF *et al.* (1959) *Derm. Wschr.*, **140**, 902.

Bulgarian cement only rarely contains chromates. The alkaline reaction and mechanical irritation is thought to be the cause of dermatitis. Positive patch tests were elicited in a very small percentage of the workmen. In these cases positive tests were found against other allergens that are not present in the cement. Positive patch tests were elicited in patients who had been in contact in the past with imported cement. The percentage of positive patch tests in over 600 men (Potassium bichromate 0.5% and 1%, cement as such and hydrarg. perchlor 1%) was very much smaller than reported from other countries. The only proved case of contact dermatitis due to chromates constitutes 0.15% of the total number investigated. In other countries the percentage seems to be between 20–25%. J. M.

UNUSUAL LOCALIZATION OF CHRONIC DISCOID LUPUS ERYTHEMATOSUS. H. HEKELL and A. MAYER. (1959) *Derm. Wschr.*, **140**, 934.

Nine cases from a total of over 1500 showed "atypical" localization: mainly on the trunk, palms, soles, extensor surfaces of extremities, as well as in one case of conjunctiva and limbus. The authors feel that these cases are particularly liable to develop systemic disease. J. M.

TREATMENT OF PENICILLIN ALLERGY WITH PENICILLINASE. W. LINDEMAYR and O. BERKOVEC. (1959) *Derm. Wschr.*, **140**, 940.

Four patients were treated very successfully with i.m. injections of penicillinase in a dosage of 400,000–800,000 units, which were repeated once or twice at 2–4-day intervals. The authors believe that depot preparations of penicillin are responsible for the increase of reactions presenting a picture of serum sickness. J. M.

THE PROBLEM OF RECURRING FACIAL ERYSIPELAS. E. NAHMMACHER. (1959) *Derm. Wschr.*, **140**, 957.

Three patients were admitted to hospital with the above diagnosis but were found to suffer from parotitis granulomatosa which is probably closely connected with the Melkersson-Rosenthal syndrome. The diagnosis was confirmed histologically in 2 cases. J. M.

CUTANEOUS MANIFESTATIONS OF LEUKAEMIA. H. E. MICHELSON. (1959) *Derm. Wschr.*, **140**, 981.

A valuable survey according to a lecture given by the late Professor Felix Pinkus. J. M.

RHODAMIN B AS A TRICHOLOGICAL DIAGNOSTIC AID. K. SCHEIBNER. (1959) *Derm. Wschr.*, **140**, 1006.

The dye Rhodamin B colours hair and the inner root sheath in paraffin sections in an alcohol fast manner. One per cent aq. solution is used and will show up mechanical and chemical damage of hair particularly after cold wave treatment. J. M.

HYPERKERATOSIS TRAUMATICA MARGINIS CALCIS. M. MANOK. (1959) *Derm. Wschr.*, **140**, 1012.

The author postulates that the common hyperkeratosis of the heel margins which may extend to the entire heel and show fissures is being provoked by wearing of the sandal type of footwear. J. M.

PSORIASIS OF MUCOUS MEMBRANES. H. J. SCHUPPENER. (1959) *Derm. Wschr.*, **140**, 1030.

The criteria for diagnosis are simultaneous development and disappearance with the cutaneous manifestations, as well as the histological picture.

Involvement of the mucous membranes (eyes and oral mucosa) is only exceptionally found in psoriasis vulgaris but is relatively more common in exudative psoriasis.

One case is described in a female aged 50 where the oral mucous membrane was involved. The patient suffered from severe exudative psoriasis. J. M.

COMPARATIVE HISTOPATHOLOGICAL STUDIES OF THE ACUTE AND CHRONIC TYPE OF MUCO-CUTANEOUS OCULAR SYNDROMES AND ERYTHEMA MULTIFORME. KASUKE ITÔ. (1959) *Derm. Wschr.*, **140**, 1054.

The acute type (Fuchs syndrome, ectodermosis erosiva plurorificialis [Fiessinger-Rendu], Stevens-Johnson syndrome) shows histological changes in the upper and lower strata of the cutis and also vascular inflammatory signs.

Most of the changes in the chronic type (Behcet's syndrome) were present in the deeper strata of the dermis whilst in erythema multiforme the upper layers of the cutis were involved. J. M.

SOFT X-RAY THERAPY IN EXTENSIVE MALIGNANT DISEASE OF THE SKIN. N. KLÜKEN. (1959) *Derm. Wschr.*, **140**, 1062.

The advantages of low voltage therapy as opposed to conventional radiation in the treatment of "problem cases" (localized over cartilage or bone as well as penile carcinoma and melanoma) are described. J. M.

FISTULAE OF THE LIPS AND ANGLES OF THE MOUTH. G. LEMKE. (1959) *Derm. Wschr.*, **140**, 1086.

Only the hereditary type in paramedian portion of the lower lips is usually described. The other varieties situated more laterally are ignored in most dental and dermatological manuals with the exception of R. Sutton's jr. Textbook (1956).

Two cases are described—one with and one without angular cheilitis. The lesions presented as puncta at the angles of the mouth and the fistulae were demonstrated radiologically. The second patient showed also evidence of the Melkersson-Rosenthal syndrome.

There was no evidence of familial incidence in either case. The pathogenesis is unknown and the lesions usually constitute only a cosmetic disability. Treatment is surgical and the author feels that this condition may easily be overlooked. J. M.

SPECTACLE FRAME DERMATITIS. H. WILDE. (1959) *Derm. Wschr.*, **140**, 1089.

Four female patients developed dermatitis at the site of contact with plastic spectacle frames. Patch tests with 0.5% formalin were positive.

The affected parts healed when the offending spectacles were replaced by metal frames and the dermatitis recurred when contact with the original spectacles was resumed. J. M.

ERUPTIONS CAUSED BY ORAL ANTIDIABETIC DRUGS. H. KRESBACH. (1959) *Derm. Wschr.*, **140**, 1091.

A male middle-aged diabetic developed an erythema figuratum-like widespread eruption after taking Tolbutamide for 2 years.

The eruption persisted for 6 weeks after the drug was withdrawn and was reproduced after disappearance when a test dose of $\frac{1}{4}$ tablet was given. J. M.

CALCIUM AND POTASSIUM MEASUREMENTS IN THE SERUM OF DERMATOSES. 1st PART —COMPARATIVE METHODS. A. ST. V. MALLINCKRODT-HAUPT and H. V. MALLINCKRODT. (1959) *Derm. Wschr.*, **140**, 1110.

Calcium and potassium estimation in the human serum were made by different methods in the same sample. The role of the deproteinization was also evaluated during the calcium estimation.

The chemical-titration (Kramer-Tisdall) as well as the flame-photometric methods were used. The results were statistically evaluated.

There was no appreciable difference in the serum with or without protein. The different results in the two methods used were not statistically significant.

The potassium values were significantly lower when the flame photometric method was used. J. M.

CLINICAL PICTURE AND THERAPY OF MELANOMATA. R. KOCH. (1959) *Derm. Wschr.*, **140**, 1117.

Reviewed 29 own cases over 5 years. Treatment by radiation alone, radiation followed by operation or operative measures with subsequent radiotherapy were evaluated.

Results in primary tumours without metastases appeared to be equal irrespective which of the above methods were used. Three patients out of 22 had died after 5 years.

Radiotherapy details as follows:

Total dose of 9000 r "contact-Chaoul" (daily doses of 500 r, focal distance 5 cm., 4 mA, 60 kV.).

If operative treatment, then followed by 9000 r X-rays or 4500 r radiation first followed by "cold caustic destruction" and the wound is then treated immediately with another dose of 4500 r. J. M.

INFLUENCE OF MOUNTAIN CLIMATE ON CONSTITUTIONAL ECZEMA. F. FUCHS and G. HENTSCHEL. (1959) *Derm. Wschr.*, **140**, 1138.

Almost 400 patients were treated for a period of about 6 weeks at an altitude of 3000 ft. The red blood cell count and haemoglobin increased and most patients improved temporarily and some for a considerable period of time. J. M.

THE AETIOLOGY OF KNUCKLE PADS. W. P. HERRMANN. (1959) *Derm. Wschr.*, **140**, 1166.

Knuckle pads arise in predisposed individuals not unlike the polyfibrose héréditaire of Touraine. Trauma is only of secondary importance.

The author describes a family with multiple pads over the knuckles as well as knees. Histologically he found proliferation of the connective tissue with marked callus formation. Another patient showed formation of pads due to repeated trauma without evidence of callosities. J. M.

TREATMENT OF INFECTIVE SKIN CONDITIONS WITH ECOMYTRIN OINTMENT. H. THEISEN. (1959) *Derm. Wschr.*, **140**, 1190.

Forty previously untreated cases were evaluated: mainly impetigo, impetiginized eczema, infected dysidrosis, folliculitis barbae, etc. This wide spectrum combination of antibiotics (amphotycin and neomycin) in emulsifying base is well tolerated. Healing was completed in most cases within 5-9 days.

Neither of the antibiotics is likely to be used parenterally. J. M.

"FAMILIAL PERLÈCHE" MIMICKED BY HEREDITARY BILATERAL ANGULAR FISTULAE. M. EISSNER. (1959) *Derm. Wschr.*, **140**, 1192.

Father and son suffered from recurrent impetigo contagiosa of the face which was preceded by angular cheilitis. Hereditary fistulae of the angles of the mouth were found to be the cause of the cheilitis. Excision of the son's fistulae were followed by complete regression of the "perlèche". J. M.

SPONTANEOUS TRICHOPHYTOSIS IN WHITE LABORATORY MICE. F. HAUFE. (1959) *Derm. Wschr.*, **140**, 1196.

Eight hundred and seventy white mice from various laboratories were examined. Fifteen were found to have mycotic infections. *T. mentagrophytes* and *T. rubrum* were cultured. *T. quinqueannum* was commonly incriminated in the past although *T. mentagrophytes* has recently been identified in white mice.

The most frequent site was the back of the animals with smaller lesions near the eyes, the muzzle area and between the ears. Alopecia and inflammatory changes were present with a certain amount of scaling of the skin. Occasionally erosions were found. The animals appeared to be in good shape although they were inclined to scratch and rub the affected parts a good deal.

It is postulated that the mice may acquire the infection through contact with other laboratory animals, e.g. guinea-pigs but trichophyton may well exist in an endemic form. J. M.

PSYCHOLOGICAL COMPONENTS IN CHRONIC URTICARIA. BENNETT KRAFT and DAVID L. BLUMENTHAL. (1959) *Acta allergol.*, **13**, 469.

Patients with chronic urticaria find difficulty in expressing anger or recognizing hostile feelings to any significant extent. H. T. H. W.

A STUDY OF CONTACT DERMATITIS DUE TO PENICILLIN. GH. NASTASE and M. MUNTEANU. (1959) *Acta allergol.*, **13**, 476.

Seven cases of dermatitis were seen in a factory manufacturing penicillin. A change in intestinal flora apparently preceded the development of penicillin allergy. H. T. H. W.

THE ROLE OF INHALANTS IN INFANTILE ECZEMA. MM. M. LELONG, J. SCLAER, J. VIALATTE, P. GRENET, MMes. D. BRUNET-LANGOT and R. LAGRUE. (1959) *Acta allergol.*, **13**, 483.

Inhalants played a larger part than food allergies in the development of infantile eczema. Desensitization with inhalant allergens gave encouraging results. H. T. H. W.

ALLERGIC SENSITIVITY TO EOSIN. C. D. CALNAN. (1959) *Acta allergol.*, **13**, 493.

Fluorescein derivatives are the only important sensitizers in lipstick dermatitis. Paper chromatography of eosin from four different sources showed more than one fluorescent component in each. The detection of the responsible allergen in each case presents great practical difficulty. H. T. H. W.

BACTERIAL ALLERGY AND PHOTOSENSITIVITY. JEAN MEYER. (1959) *Acta allergol.*, **13**, 417.

A progressive increase in the dose of an intradermal vaccine produces a correspondingly increased area of erythema. Progressively longer exposures to U.V.L. produce a similar effect. In cases of specific allergy the initial threshold is usually but not invariably low, while a small increase in the provocative dose causes a disproportionate increase in erythema. H. T. H. W.

ATTEMPTS AT PASSIVE TRANSFER IN ALLERGIC ECZEMA. CARLO LUIGI MENEGHINI and LUCIANO LEVI. (1959) *Acta allergol.*, **13**, 432.

Attempts at passive transfer were made with leucocytes or cellular material from lymph nodes of patient with allergic contact dermatitis. In the majority of cases the tests were negative. H. T. H. W.

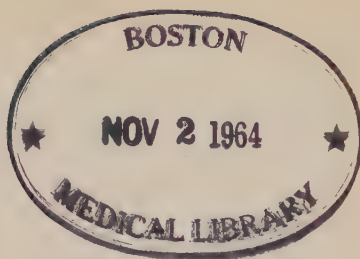
BLOOD GROUPS AND ENDOGENOUS ECZEMA. VON HARRY DORN. (1959) *Acta allergol.*, **13**, 442.

Although a study of a few hundred cases is insufficient to give a confident opinion, there appears to be some association between blood groups and allergic skin diseases. H. T. H. W.

URTICARIA DUE TO FLUORIDE. G. L. WALDBOTT. (1959) *Acta allergol.*, **13**, 456.

In six cases of urticaria, fluoride (usually in drinking water) was the major or sole cause.

H. T. H. W.



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